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BRITISH MEDICAL JOURNAL

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THE TREATMENT OF BLOOD DISORDERS WITH A.C.T.H. AND CORTISONE

A PRELIMINARY REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE PANEL* ON THE HAEMATOLOGICAL APPLICATIONS OF A.C.T.H. AND CORTISONE

The Panel appointed by the Medical Research Council to study the action of A.C.T.H. and cortisone in the treatment of diseases of the blood selected as suitable for trial, in the first instance, the conditions thrombocytopenic purpura and haemolytic anaemia. Later the trials were extended to include cases of refractory anaemia. In addition the Panel supported a limited trial in leukaemia and allied states, mainly in the Department of Haematology, Royal Infirmary, Manchester, where some preliminary work had already been done. No attempts were made at controlled trials, for, apart from leukaemia, the diseases treated are uncommon, and it seemed more important first of all to determine whether there were grounds for further trial. When necessary, patients received blood transfusions during the period of hormone therapy. The great majority of the patients were under the care of members of the Panel, who were personally responsible for making the diagnosis, controlling the treatment, and summarizing the observations.† The present paper is a report on 88 patients treated during the first year of the trial.

Drugs Used and Dosage

In all, 88 patients were treated, 55 with A.C.T.H. alone, 21 with cortisone alone, and 12 with both, usually in successive courses. The A.C.T.H. was given intramuscularly, as a rule every six hours. The usual course consisted of about 1 g., given in a period of 10 days, though some patients received considerably more. Children under 16 were usually given about 40 mg. a day for 10–12 days. Cortisone was usually given intramuscularly, though in a few patients it was given orally. Adults received a minimum of 1.5 g. in 10 days, and many received 2.5–3.5 g. over a period of 15–30 days.

Criteria of Improvement

Results are classified as follows (see Table). A *good response* implies that there was obvious clinical improvement combined with a decisive change in the relevant laboratory findings—blood count, bone marrow, serology, etc. The term "good response" was preferred to "complete response," because a complete return to normal was not insisted on. The term *partial response* implies either a measurable clinical improvement or some change for the better in the laboratory data. Thus a cessation of purpura and bleeding in thrombocytopenic purpura, either alone or accompanied by an improvement in the bleeding-time but not associated with a rise in the platelet count, is defined as a partial response. The temporary euphoria which occurs so characteristically in patients treated with A.C.T.H. and cortisone was not classified as a response to treatment. Responses were further subdivided into immediate, where they lasted only during the period of therapy, and prolonged, where they were maintained for at least a month after stopping treatment.

Summary of Responses to A.C.T.H. or Cortisone

	No. of Cases	No Response	Good Response		Partial Response	
			Immediate*	Prolonged†	Immediate*	Prolonged†
Haemolytic anaemias:						
Acquired (idiopathic and symptomatic)	11	3		3	3	2
Congenital	6	6				
Nocturnal haemoglobinuria	2	2				
	19					
Purpura:						
Idiopathic thrombocytopenia	10	5	1	1	3	
Toxic	4	1		2	1	
	14					
Leukaemia:						
Acute and subacute myeloid	16	12		1	3	
Acute lymphatic	12	7			4	1
Chronic lymphatic	1	1				
Acute monocytic	5	5				
Unclassified leukaemia	3	3				
Myelomatosis	2	2				
Reticulosarcoma	1	1				
	40					
Miscellaneous:						
Aplastic anaemia	2	2				
Refractory with active bone marrow	5	5				
Myelosclerosis	5	4			1	
Panhaematopenia	3	3				
	15					
Total No. of cases	88	62	1	7	15	3

* "Immediate" means during treatment only.
† "Prolonged" means maintained for at least one month after stopping treatment.

Results

The cases treated fall conveniently into four main groups: haemolytic anaemia, thrombocytopenic purpura, leukaemia, and miscellaneous.

Haemolytic Anaemia

There were 11 patients, all adults, with acquired haemolytic anaemia: 9 were classified as idiopathic and 2 as symptomatic, associated with acute disseminated lupus erythematosus and reticulosarcoma respectively. The direct Coombs test was positive in 9 of the 11 cases. Eight of these 11 patients showed some favourable response to treatment, and in 5 of these 8 the improvement was maintained for at least a month after stopping treatment. However, the response was

Members of the Panel: Professor L. J. Witts (chairman), Dr. C. J. C. Britton, Professor L. S. P. Davidson, Professor L. J. Davis, Professor A. Haddow, Sir Lionel Whitby, Dr. J. F. Wilkinson, Dr. P. L. Mollison (secretary).

†Three of the patients were treated by Drs. J. D. Nabarro and W. Walker.

really good in only 3 cases; in these three, improvement was maintained for more than six months. In the cases that showed the best haematological response the direct Coombs test became negative in one case but remained positive in another. Among 5 cases which responded partially the direct Coombs test became weaker (or negative) in 3. Thus some patients responded well although the direct Coombs test remained positive. Four of the 11 patients had been ill for four months or less, but their response in no way differed from that of the more chronic cases. The response to A.C.T.H. or cortisone did not appear to depend on the previous clinical or haematological findings; and neither a short history nor a positive Coombs test implied that the response would be favourable.

Six patients with hereditary spherocytosis (congenital acholuric jaundice) and 2 patients with paroxysmal nocturnal haemoglobinuria did not appear to benefit in any way from treatment with A.C.T.H. or cortisone.

Thrombocytopenic Purpura

Fourteen patients—1 man and 13 women—were treated; 4 were considered to be toxic—that is, secondary to gold therapy, etc.—and 10 were classified as essential. Five of the patients had been ill for four months or less.

Amongst the 10 cases of essential thrombocytopenic purpura, 2 had previously undergone splenectomy without improvement; neither of these 2 patients responded to treatment with cortisone. Of the remaining 8 patients who had not undergone splenectomy 5 improved during treatment, but 4 of these relapsed when it was stopped. The only patient with essential thrombocytopenic purpura who remained better for more than a month after treatment was stopped was a man who had been ill for only five weeks before treatment was started.

Among the 4 cases of toxic purpura 1 had previously undergone splenectomy. This was a patient whose illness was attributed to the ingestion of artists' pigments. During cortisone therapy there was steady improvement and the patient appeared to be cured—that is to say, no relapse was noted during the next nine months. Of the remaining 3 patients with toxic thrombocytopenic purpura only 1 showed any response to hormone treatment, and she relapsed again as soon as treatment was stopped. This patient had exfoliative dermatitis, and it is noteworthy that in her, as well as in the previously mentioned patient with toxic purpura who did well, the rise in blood platelets occurred after the end of the course of treatment.

Leukaemia and Allied Conditions

This group of 40 cases consisted almost entirely of patients with acute or subacute leukaemia (36 cases). Of these 36, 16 were classified as myeloid (8 children, 8 adults), 12 as lymphatic (9 children, 3 adults), and 5 as monocytic (1 child, 4 adults); 3 were unclassified types (2 children, 1 adult).

Out of 20 children with acute leukaemia 14 showed no response, though 3 of these died after less than one week's treatment; 4 showed a partial response during treatment, and in 2 further cases improvement was maintained for more than one month after stopping treatment. However, in only 1 of them could the remission be described as "complete."

Out of 16 adults, all with acute leukaemia, 13 showed no response to treatment, though 2 of these received less than one week's treatment; 3 showed a partial response only during the period of treatment. There were no sustained remissions.

One patient with chronic lymphatic leukaemia, 2 patients with myelomatosis, and 1 patient diagnosed as suffering from giant-cell reticulosis (? reticulosarcoma) showed no response to treatment.

Miscellaneous

This group consisted of 15 patients with different forms of refractory anaemia. Two had aplastic anaemia with hypocellular marrow; 5, refractory anaemia with cellular marrow; 5, myelosclerosis; 3, panhaematopenia with negative direct Coombs test. Fourteen of these 15 patients showed no favourable response; the remaining patient, a woman with myelosclerosis, improved during treatment but relapsed afterwards.

Side-effects

No fatalities were attributed to the treatment, but there were some troublesome side-effects, apart from the common "moon-face"; these included oedema (10), hypertension (5), psychoses (5), glycosuria (3), gluteal abscess or sepsis (2), congestive failure (1), dysuria (1), headache and vomiting (1).

Discussion

The experience of the Haematology Panel with A.C.T.H. and cortisone is relatively small, in spite of the fact that the Panel includes a number of workers in different centres. Nevertheless, it accords with other comparable series of cases which have recently been published (Limarzi *et al.*, 1951; Mote, 1951; Rosenberg *et al.*, 1951; Rosenthal *et al.*, 1951; Wintrobe *et al.*, 1951). The general impression obtained so far is that A.C.T.H. and cortisone, as at present used, are not likely to have an important part to play in the treatment of disorders of the blood. The best results are obtained in acquired haemolytic anaemia and in thrombocytopenic purpura. Here the hormones can promote remissions in a proportion of cases, though the results are uncertain and unpredictable and sometimes of brief duration. It could be argued that remissions are no more frequent than might be expected in the natural course of these illnesses, but this seems unlikely. The Panel has considered the possibility of a controlled trial of A.C.T.H. and cortisone in purpura and the haemolytic anaemias, but the cases are so infrequent and dispersed, and moreover so variable, that it does not seem practicable.

In the aplastic and refractory anaemias, with the possible exception of cases in which there is a haemolytic component, it can now be said that in our experience A.C.T.H. and cortisone have little or no therapeutic effect.

In leukaemia it seems that therapeutic effects are largely confined to the acute types, and more particularly to acute leukaemia in childhood; and here our success has been a good deal less than has been reported from some American centres. Complete remission was obtained in only 1 out of 36 cases of acute leukaemia: this was in a child who died six months later; some regression of symptoms was observed in 8 other cases. All these effects are temporary, though there is evidence that the total duration of life may be increased in some cases by a few weeks or months. It must be said that the case for the employment of A.C.T.H. and cortisone in leukaemia and allied conditions is not a strong one.

Summary

A.C.T.H. and cortisone have been used in 88 patients with diseases of the blood.

A.C.T.H. and cortisone appeared to produce remissions in a proportion of cases of acquired haemolytic anaemia and thrombocytopenic purpura, but the results were uncertain and unpredictable.

A.C.T.H. and cortisone produced complete remission in only 1 out of 36 cases of acute leukaemia and partial improvement in another 8. Effects in all cases were temporary.

No effects were produced in aplastic and refractory anaemias.

The cortisone used in this investigation was supplied by the Medical Research Council, and was in part derived from a gift

from Messrs. Merck and Co., made jointly to the Medical Research Council and the Nuffield Trust.

REFERENCES

Limarzi, L. R., Paul, J. T., and Best, W. R. (1951). *J. Lab. clin. Med.*, **38**, 922.
Mote, J. R. (1951). *Proceedings of the Second Clinical A.C.T.H. Conference*. Vol. 2, Therapeutics. London.
Rosenberg, I. N., Cleroux, A. P., Raben, M. S., Payne, R. W., and Astwood, E. B. (1951). *Arch. intern. Med.*, **88**, 211.
Rosenthal, M. C., Saunders, R. H., Schwartz, L. I., Zannos, L., Perez Santiago, E., and Dameshek, W. (1951). *Blood*, **6**, 804.
Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J., and Samuels, L. T. (1951). *Arch. intern. Med.*, **88**, 310.

THE SENSITIVITY OF ACTINOMYCES ISRAELI TO ANTIBIOTICS

BY

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Although sulphonamides have some effect in actinomycosis, penicillin has much more, and is now the standard treatment for this disease. There are nevertheless three reasons for inquiring into the possible usefulness of later antibiotics: they may conceivably be even more effective, a given patient's strain of *Actinomyces israeli* may be or become abnormally resistant to penicillin, or the patient may be intolerant of this drug.

There are records of the treatment of small numbers of cases of actinomycosis with antibiotics other than penicillin. Streptomycin was used successfully by Costigan (1947) in one atypical and not fully confirmed case, by Pemberton and Hunter (1949), who gave the drug by the mouth to a patient with a lesion in the rectum, by Torrens and Wood (1949), who treated three authenticated cases by a prolonged course of injections, and by Lambert (1951). Some of these patients had previously been given penicillin with no or only temporary benefit. Pulaski and Seeley (1948) mention a case in which the organism became resistant to the drug and the disease progressed: that a high degree of such resistance can develop *in vitro* has been shown by Boand and Novak (1949). All clinical reports on the response of the disease to aureomycin are enthusiastic: Wright and Lowen (1950) cured one case, McVay, Guthrie, and Sprunt (1951) three, Grant (1951) one, and Kelly (1951) one, which had previously not responded at all to streptomycin or penicillin, and only temporarily to chloramphenicol. Chloramphenicol was employed successfully together with penicillin and sulphadiazine in one patient by Littman, Phillips, and Fusillo (1950). There are also single case reports of the successful treatment of *Nocardia asteroides* infection with streptomycin, penicillin, and sulphadiazine (Jacobson and Cloward, 1948) and of *Nocardia madurae* infection with aureomycin and "diasone" (Thompson and Wax, 1950).

Only two of these papers mention *in vitro* tests of sensitivity to the drug. Littman *et al.* tested their own strain and five obtained from Holm against chloramphenicol, and found them to be inhibited by 0.5–3 μg./ml. McVay *et al.* say that tests showed their strains to be sensitive to aureomycin, but the only figure given is failure of inhibition by 50 μg./ml. Three strains of "*Actinomyces bovis*" (two human and one bovine) were tested by Strauss, Kligman, and Pillsbury (1951) against five antibiotics and six other drugs: concentrations as high as 200 μg./ml. of streptomycin, 100 μg./ml. of aureomycin, and 50 μg./ml. of penicillin were required to inhibit growth completely. Such results, if accepted at their face value, would preclude any hope of useful therapeutic effect, and they may be attributable to an inappropriate choice of method. Incubation was for ten days, and the medium contained thioglycollate, which is known to inactivate penicillin.

In view of this paucity of reliable information it seemed desirable to test an adequate number of strains by a uniform technique to determine their *in vitro* sensitivity to all available antibiotics. Such tests are usually, although not infallibly, a guide to therapeutic effect, and they should serve to indicate whether sensitivity is uniform or subject to strain variation.

Experimental

Strains of A. israeli.—Twelve strains were tested: six were personally isolated from cases of actinomycosis in this hospital (three of these are now in the National Collection of Type Cultures, their names and N.C.T.C. numbers being Burnett 8440, Hyder 8439, and Maslin 8441); three were obtained from the National Collection of Type Cultures (Bishop 8047, Burton 7504, and West 6831); and three were cultivated from granules in excised tonsils: these last had all the morphological and cultural characters of *A. israeli*.

Method.—Freshly made solutions of the antibiotics were added to ox heart extract peptone broth, *p*H 7.4, in bulk, and doubled dilutions prepared therefrom in bulk, each then being tubed in 5-ml. volumes. These tubes were inoculated with one drop (approximately 0.02 ml.) of a fine suspension of a fully grown culture, prepared by agitation when this sufficed to break up colonies, or if necessary by grinding the growth with the rounded end of a thick glass rod in a small tube. The size of the inoculum was not deliberately standardized in terms of opacity, but was nevertheless reasonably uniform, and no whole colonies or large fragments thereof were included; these have been shown by Holm (1948) to affect the result of such tests with penicillin. The cultures were incubated anaerobically with 5% CO_2 in McIntosh and Fildes jars for five days. Controls all gave profuse growth in this time in the form of a deposit of compact colonies or floccules.

Results.—The minimum completely inhibitory concentrations of each of five antibiotics for each strain are stated in the Table. Commonly one, and sometimes two, lower dilutions reduced the amount of growth below that in the control. There are no extreme strain variations in sensitivity: penicillin is the most active and streptomycin the least, the three newer antibiotics occupying an intermediate position. Identical tests, not recorded here in detail, were made with five strains of *A. naeslundi* (Thompson and Lovestedt, 1951) cultivated from normal mouths, and gave closely similar results. Sensitivity to antibiotics is therefore apparently not a character distinguishing between pathogenic and non-pathogenic species in this as in some other genera—for example, *Bacillus*.

Minimum Concentrations (μg./ml.) of Five Antibiotics Inhibiting Growth of 12 Strains of Actinomyces israeli. (Figures are Numbers of Strains Inhibited by Each Concentration)

	0·03	0·06	0·12	0·25	0·5	1	2	4	8	16	32	64
Penicillin*	2	3	6	1								
Streptomycin								1	3	4	2	2
Aureomycin						1	3	5	3			
Chloramphenicol						2	4	6				
Terramycin					1	4	5	1	1			

* Concentrations of this antibiotic are units/ml. (1 unit = 0·6 μg.).

Discussion

So far as is known, only one of the patients from whom these strains were cultivated had previously been treated with penicillin, and neither this nor any other strain

displays any unusual resistance to the drug. Since 1944 I have similarly examined 18 other strains and found the minimum inhibitory concentration of penicillin for them to vary only between 0.02 and 0.14 unit/ml. On the other hand, unsuccessful treatment may be accompanied by an increase in resistance: the inhibitory concentrations for two of these strains rose from 0.03 unit/ml. in each case to 0.2 and >0.5 unit/ml. In such patients an alternative treatment may be indicated.

These findings and items of clinical evidence already cited suggest that any of the four newer antibiotics in general use may be effective, although it might perhaps be unwise to rely on streptomycin unless the strain were proved by test to be in the more favourable part of the range of sensitivity to this antibiotic. It should be noted that the *p*H change produced by an atmosphere containing added CO_2 is unfavourable to streptomycin, and allowance should be made for this in interpreting these results. Penicillin and streptomycin have been shown to act synergically on other species, and might with possible advantage be used together in a patient needing vigorous treatment. Of the three newer antibiotics terramycin is rather more active than aureomycin or chloramphenicol as judged by mean inhibitory concentrations.

The results with these three drugs should also be viewed in the light of their relative stabilities. Chloramphenicol and terramycin are both stable; aureomycin is so unstable in an alkaline medium that it loses the greater part of its activity in ordinary broth at 37° C. during the first day of incubation. (This process may have been somewhat retarded in the present tests by the addition of CO_2.) The observed result of any test with it consequently varies with the period of incubation, and becomes progressively more unfavourable as this is prolonged. The slow growth of *A. israeli*, necessitating incubation for five days, presents conditions highly unfavourable to the action of aureomycin, and it was not anticipated before these tests were made that it would perform so well: indeed, it seemed that some other form of test might have to be devised to obtain a true assessment of its activity. It would be more appropriate, for instance, to add further antibiotic to the cultures daily in order to restore the original concentration. If this were done and conditions *in vivo* during therapy thus more closely imitated (without invalidating comparison with the action of a more stable antibiotic) it might prove that the maintained concentration of aureomycin required to inhibit the growth of *A. israeli* is considerably lower than that observed in the present tests. The uniformly successful results of reported clinical trials also suggest a high degree of activity.

Summary

The mean minimum inhibitory concentrations (μg./ml.) of five antibiotics for twelve strains of *Actinomyces israeli* were found to be: penicillin 0.06, streptomycin 23.7, aureomycin 4.2, chloramphenicol 2.8, and terramycin 2.2.

The greater part of the technical work connected with the isolation and maintenance of these strains and the performance of the tests was carried out by Miss Pamela M. Waterworth.

REFERENCES

Boand, A., and Novak, M. (1949). *J. Bact.*, **57**, 501.
Costigan, P. G. (1947). *Canad. med. Ass. J.*, **56**, 431.
Grant, R. (1951). *J. oral Surg.*, **9**, 334.
Holm, P. (1948). *Acta path. microbiol. scand.*, **25**, 376.
Jacobson, J. R., and Cloward, R. B. (1948). *J. Amer. med. Ass.*, **137**, 769.
Kelly, H. H. D. (1951). *British Medical Journal*, **2**, 779.
Lambert, A. (1951). *Sem. Hôp. Paris*, **27**, 1477.
Litman, M. L., Phillips, G. E., and Fusillo, M. H. (1950). *Amer. J. clin. Path.*, **20**, 1076.
McVay, L. V., Guthrie, F., and Sprunt, D. H. (1951). *New Engl. J. Med.*, **245**, 91.
Pemberton, H. S., and Hunter, W. R. (1949). *Lancet*, **1**, 1094.
Pulaski, E. J., and Seeley, S. F. (1948). *J. Lab. clin. Med.*, **33**, 1.
Strauss, R. E., Kligman, A. M., and Pillsbury, D. M. (1951). *Amer. Rev. Tuberc.*, **63**, 441.
Thompson, F. R., and Wax, W. V. (1950). *N.Y. St. J. Med.*, **50**, 1499.
Thompson, L., and Lovestedt, S. A. (1951). *Proc. Mayo Clin.*, **26**, 169.
Torrens, J. A., and Wood, M. W. W. (1949). *Lancet*, **1**, 1091.
Wright, L. T., and Lowen, H. J. (1950). *J. Amer. med. Ass.*, **144**, 21.

THE DIAGNOSIS OF INTERSEX

BY

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The problem of the infant of doubtful sex is one which occasionally faces every clinician who concerns himself with children's work, and yet, in spite of the importance of a correct decision, it is still impossible to obtain guidance on this matter from the ordinary textbooks. Too often the decision is postponed to see which way the child will develop; the parents are left without guidance, and their natural anxiety is communicated to the child, who is thus in danger of becoming a psychological as well as a surgical problem.

The present communication, which is based upon experience at the Hospital for Sick Children, Great Ormond Street, and upon a review of the literature which has appeared since the publication in 1937 of H. H. Young's classical monograph, is concerned with the diagnosis and with the probable outcome in various types of intersexuality. A classification is employed which has as its basis the histological appearance of the gonads: intersex males and intersex females have respectively testicles and ovaries; true hermaphrodites have gonadal tissue of both types. But it is not claimed that the nature of the gonad infallibly indicates the "genetic" sex, nor is it intended here to advance any theory of causation.

Intersex Females (Female Pseudohermaphrodites)

(a) Intersex Females with Hyperplasia of the Adrenal Cortex

Most intersex females in whom an adequate investigation has been carried out have proved to be suffering from adrenal cortical overactivity, and it is now commonly supposed that adrenal hyperplasia during foetal life is responsible for the deformity. It is suggested that development of a genetic female proceeds normally during the early weeks, the ovaries differentiate, and under their influence the Müllerian ducts evolve in the usual manner, forming uterus and Fallopian tubes. Some time after the twelfth week, however, the virilizing hormones of the adrenal cortex deflect the normal line of development; the vagina does not push downwards, nor does the urogenital sinus widen out below it; the phallus grows more rapidly and the urethral folds tend to fuse. At birth, therefore, the infant is found to have a phallus approaching in size a penis, with some degree of hypospadias. Most commonly the urethral meatus is represented by a rather wide opening in the perineum, and the vaginal orifice lies just within (see Fig. 1). In lesser degrees the vagina opens externally through a narrow introitus; in the more severe, closure of the urethral folds has proceeded to a point which brings the urethral meatus well up the phallus, and the vagina can be discovered only by endoscopy. In the latter type the labio-scrotal folds may also fuse to form an empty but otherwise normal scrotum. One case is on record (Wilkins, 1950) in which a penis was fully formed with a terminal meatus.

The action of the adrenal cortical hyperplasia does not cease at birth and there is commonly a continuing virilization: somatic growth is accelerated, and ossifi-

cation and epiphysial fusion occur prematurely. Muscularity and hirsutism are evident long before they would be expected in a boy of the same age, although the relative proportions of shoulders and hips may still suggest a female origin. The phallus continues its rapid growth, and frequent erections may be troublesome. At puberty the breasts fail to develop, and the adrenal over-activity is, with very rare exceptions, sufficient to suppress all evidence of an ovarian cycle. Only one definite case of urethral menstruation has been reported in this group (Everidge, 1945); others (for example, Chanis, 1942) are open to question. Hypertension may be present in the older cases; but the condition is not incompatible with a normal span of life.

FIG. 1.—The anatomy of an intersex female (hormonal type). The diagram shows the vagina opening at the characteristic level—near the perineal membrane. The upper vagina, uterus, and tubes are normally formed and symmetrical. The urethra is here shown opening well forward on the shaft of the penis, and the labio-scrotal folds have united.

The diagnosis of this hormonal sex reversal depends upon the recognition of the characteristic anatomy in conjunction with the signs of adrenal cortical hyperplasia. When the vagina is not evident exteriorly it can be demonstrated with the urethroscope: as the instrument is withdrawn from the bladder the absence of the verumontanum is noticed, and at approximately the level of the perineal membrane the vaginal introitus can be found. Once identified, the vagina, which is capacious and supple, can usually be entered with the instrument and the cervix visualized. By catheterization of the cervix and injection of iodoxyl *B.P.*, a hysterosalpingogram can be produced. If a laparotomy is performed, though it should not usually be necessary, an infantile uterus will be found, with normal tubes and ovaries. The latter are often cystic, but lie in their usual position and show no tendency to migrate to the inguinal region even when the scrotum has been fully formed.

Enlargement of the adrenal glands may sometimes be recognized at laparotomy, but in most cases it is the endocrine imbalance alone which betrays their disorder. The effects of precocity and virilization may be evident to superficial examination, radiographs of the wrists will demonstrate the advanced bone age, and even from the first few months of life the urinary excretion of 17-ketosteroids is considerably increased (Harris and Scowen, 1951). A familial incidence of this deformity is commonly recorded.

Many of the more severe cases in this group are raised as boys and are quite content with their lot. Their interests, activity, and libido are entirely masculine; some are happily married to women, and at least two have committed suicide because a marriage ceremony was refused by their church. It appears to be quite unjustifiable to reverse the sex of any child in this group hitherto regarded as male, and operation for the cure of hypospadias should be undertaken.

When the sex has been correctly diagnosed at birth the progressive masculinization of both body and mind may occasion a severe conflict, and cases changing to the male role of their own volition are recorded by Genitis and Bronstein (1942). Such changes can seldom be satisfactory, however, and attempts at feminization of the cases raised as girls constitute the obvious line of treatment. Surgical resection of the hypertrophied adrenals has not proved of great value; occasional successes have been reported—for example, Wilhelm (1947)—but, particularly in the prepubertal cases, recurrence has been the rule. Stilboestrol therapy alone has also been disappointing even in mild cases. The administration of cortisone results in a rapid fall in the excretion of 17-ketosteroids (Wilkins *et al.*, 1951), and the continuation of the therapy for a period of four to five months may produce breast development, regression of hirsutism, and cyclical uterine bleeding. Cessation of treatment after a short period is followed by a prompt rise in urinary 17-ketosteroids, and whether long-term therapy will produce any more permanent change has yet to be discovered. The sexual orientation of the intersex female has been fully discussed by Hinman (1951), to whose paper reference should be made for the bibliography relevant to this group.

A further possibility in connexion with the adrenal sex reversal requires consideration. In many of the reported cases the patients have died during the first few weeks of life with vomiting and dehydration. Some have been thought to suffer from pyloric stenosis. It has recently been demonstrated, however (Panos, 1950), that these infants are in fact suffering from an endocrine disturbance closely allied to Addison's disease. The serum chloride level is grossly depressed but can be restored by the administration of desoxycortone acetate: it seems that the excessive output of adrenal androgens is associated with a deficiency of the hormones concerned with electrolyte metabolism.

Many case records of intersex females have now been published; I have had the opportunity of urethroscoping five examples of this group, which have been included in the series described and illustrated by Jolly (1951). Details of one of these cases are as follows.

Case 1

The patient (Mr. Denis Browne's case), first seen by me at the age of 17, had been brought up as a boy, and the first stage of a hypospadias operation had been performed by another surgeon during childhood. Later, doubt about the true sex had arisen and further operations had been postponed. The patient continued his male upbringing, but was taken away from school before finishing his course. In childhood his growth had been advanced, but at the age of 17 he was short owing to premature epiphysial fusion. He was slight, flat-chested, and hirsute. The phallus was a little smaller than would be expected in a normal boy of the same age, and a deep mucous groove marked its under surface; there was a wide meatus in the perineum within which, by forceful retraction, could be seen two orifices. Endoscopy revealed a normal female type of urethra, a vagina, and a uterine cervix. The labial folds were large and plentifully covered with hair but not rugose, and no gonads could be palpated externally. On rectal examination a small mobile uterus could be felt; the vagina itself was not palpable. Excretion of 17-ketosteroids amounted to 51.7 mg. per 24 hours. The patient's inclinations were entirely masculine, and a penile urethra was therefore constructed. It may be remarked that the operation for repair of hypospadias which has been described by Denis Browne (1950) has the signal advantage that these extreme cases are as easily repaired as minor degrees of the deformity.

(b) Intersex Females Without Adrenal Disorder

A few cases have been reported (Cotte, 1947; Wilkins, 1950) which suggest that the intersex female type of anatomy may occur without adrenal overactivity; but such instances must be extremely rare, and it is difficult to be sure that some testicular tissue, which would bring the case into the category of the true hermaphrodites, has not been overlooked. This difficulty was illustrated by a personally observed case of a child with a well-formed penis, in whom

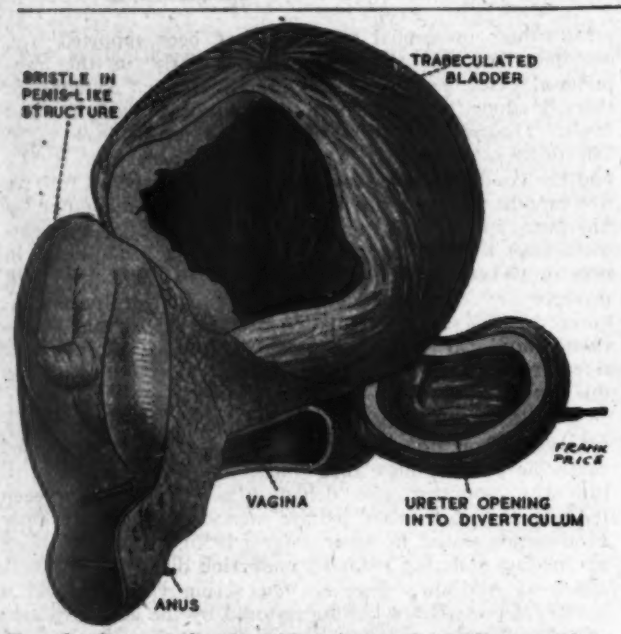

FIG. 2.—Intersex female with urinary obstruction: specimen preserved in the Museum of the Royal College of Surgeons, showing the thick trabeculated bladder with a large diverticulum into which the ureter opens, and externally the penis-like phallus.

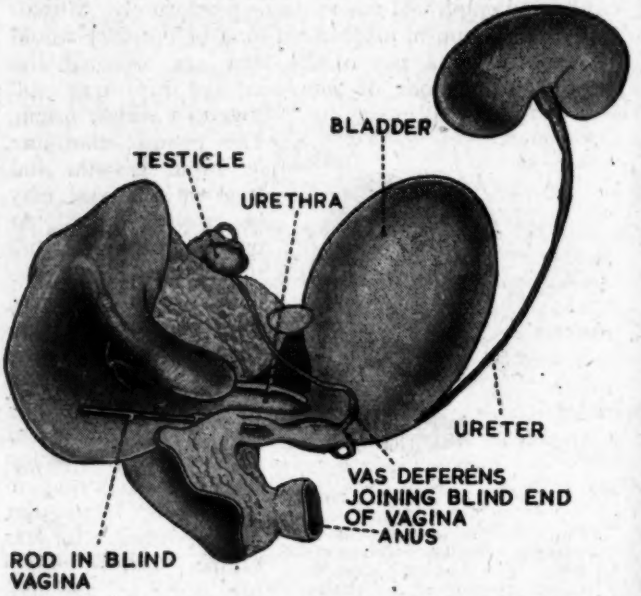

FIG. 4.—Intersex male with purely feminine external genitalia and bodily habitus: specimen preserved in the Museum of the Royal College of Surgeons. No clinical notes are available, save that the child's name was Ellen. For description of anatomy see text.

only ovarian tissue could be found, but who had previously had an inguinal operation elsewhere. There is, however, one rare but clearly defined condition in which female intersexuality is associated with urinary obstruction (Howard and Hinman, 1951). Fig. 2 shows a specimen of this type preserved in the Royal College of Surgeons: the urethra opens through a penile type of phallus, but is so extremely narrow that the bladder shows severe back pressure effects, with two large diverticula into which the ureters open. There is no scrotum, but a small orifice at the base of the median raphe on the phallus opens into a capacious vagina which is associated with normal uterus and tubes (Fig. 3).

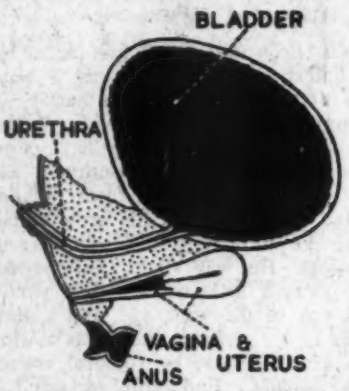

FIG. 3.—Intersex female as Fig. 2, showing diagrammatically the arrangement of the passages (see text).

Intersex Males (Male Pseudohermaphrodites)

(a) Intersex Males with Purely Feminine External Genitalia and Bodily Habitus

Many cases in this group have been recorded (Krückmann, 1937; Carlisle and Geiger, 1938; Greenhill and Schmitz, 1940; Pratt, 1940; Weisman and Schwarz, 1941; McMillan, 1942; Novak, 1943; Hain and Schofield, 1947; Bleyer, 1948; Goldberg and Maxwell, 1948; Fazen, 1949; Cook, 1950; Ward-McQuaid and Lennon, 1950; Stollmeyer and Latour, 1950; Oberthur, 1950; Wilkins, 1950; Wachstein and Scorza, 1951). These cases are always regarded as girls. The external genitalia—clitoris, labia, and vaginal orifice—appear normally female in the child, and the body develops upon the expected female lines. With the onset of puberty the breasts increase in size, but they rarely advance beyond adolescent development; pubic and axillary hair is either absent or extremely scanty, and menstruation fails to start. It is the amenorrhoea or the presence of painful inguinal lumps which brings the patient for medical examination. It is then found that the vagina ends blindly a short distance above the hymen, and exploration of the inguinal herniae or of the abdominal cavity reveals the presence of atrophic testicles. The epididymides and vasa may be rudimentary, may be altogether absent, or may be replaced by structures resembling Fallopian tubes and connected with the blind end of the vagina by minute ducts thought to represent paired uterine canals (see Fig. 4). Histologically the testicles present all the features of undescended and undeveloped organs. Spermatogenesis is absent, but Sertoli cells and the interstitial tissue are well formed; small tubular adenomata are a characteristic finding.

The majority of these individuals have lived reasonably satisfactory lives in the female role and with normal female reactions; a few have shown an excessive female libido; more have had little interest in sexual relations. Castration after puberty has produced typical menopausal symptoms and a loss of female libido. In the cases in which it has been estimated, 17-ketosteroid excretion has been low, but important adrenal hyperplasia has been described in some (Von Gierke, 1928; Healey and Guy, 1931). A familial incidence is common.

Treatment is scarcely necessary in many cases. Clearly there can be no question of altering the accepted sex, but most have required bilateral orchidectomy because of pain, and castration combined with stilboestrol therapy may increase the size of the breasts and promote the growth of normal pubic hair.

Case 2

This child (Mr. Denis Browne's case), who had the appearance of a normal and attractive little girl, was brought up for examination at the age of 3 years because her elder brother had suffered from hypospadias and the parents wished to be sure that she had no abnormalities. The external genitalia appeared normally feminine, but no uterus could be felt per rectum, the vagina was extremely short, and a smooth mobile body could be felt in each groin. At operation these bodies were shown to be testicles and to be connected to the blind end of the vagina by vasa deferentia. The child was castrated. The parents have simply been told that the child has no uterus. It is planned to give her stilboestrol therapy at puberty.

(b) Intersex Males with Masculine External Genitalia and Feminine Type of Uterus

Cases in this group have been recorded by Nilson (1939), Kozoll (1942), Patton (1948), and Keen and de Villiers (1949). In these cases again there is never any doubt about

the sex of the child or adult: the penis is normally developed, with a terminal meatus; the bodily form, hair, muscularity, and voice are all male in type. One testicle is commonly undescended, however, and a hernia is present on that side, often associated with definite pain. At operation, traction on the hernial sac brings to light the testicle and with it a muscular uterus and Fallopian tubes. The testicles are histologically normal for undescended organs, and there is no suggestion of cyclical changes in the uterus. Where the point has been investigated the uterus or vagina appears to have ended blindly at the lower end. Hysterectomy with repair of the hernia has been the usual method of treatment, and no important complications are recorded. A specimen representing this group is preserved in the Museum of the Royal College of Surgeons.

(c) Intersex Males with External Genitalia of Equivocal Sexuality

In this group, a somewhat heterogeneous one, simple inspection of the external genitalia gives rise to the suspicion of a genital abnormality, and at birth the child may be labelled either boy or girl. In the simplest cases there is merely an extreme degree of hypospadias, with a small penis, bifid scrotum, and failure or delay in the descent of the testicles. A normal verumontanum is present in some cases, but in many there is a vagina which opens into the posterior urethra or externally. In a few there is in addition a uterus, with Fallopian tubes, and the testicles are suspended from the broad ligament. In contrast to the intersex females, however, the uterus and tubes are seldom symmetrical and the vagina is usually palpable as a firm cord extending down to the posterior urethra.

In the majority of adult cases the masculine bodily form—broad shoulders, lack of subcutaneous fat, and facial hair—is preserved and the voice deepens at puberty. Occasionally, however, failure of the testicular functions results in gynaecomastia and eunuchoid proportions, as in the Klinefelter syndrome, and in those cases the excretion of pituitary gonadotrophins is considerably raised after the age of 12 or 13 (Hamblen *et al.*, 1951).

Cyclical uterine bleeding does not occur in untreated intersex males, although any slight show of blood may be interpreted as a "period" by those who believe themselves female. Uterine bleeding can be induced by intermittent dosage with stilboestrol even without castration (Ingersoll and Finesinger, 1947), a procedure which may be of value in satisfying those individuals who are determined to remain in a female role. Pyometra or less severe infections of the female genital organs may give rise to symptoms on occasion, usually after operations for hypospadias which have involved indwelling urethral catheters.

The sexual inclinations of the intersex males are perhaps the most interesting feature of the group. In cases correctly diagnosed at birth and brought up as males little trouble is experienced, even where hypogonadism gives rise to breast development at puberty and a somewhat effeminate appearance: they (Sisk and Cornwell, 1942) are glad to continue in the male role, and require only plastic surgery. When the child has been reared as a girl, however, three possible lines of psychological evolution must be considered. First, often during adolescence an evident and increasing virility may break through the tradition of his feminine education and a change of sex becomes inevitable. Secondly, the child may grow into adult life without any urgent interest in sex, aware of some abnormality, and avoiding intimate relations, but content to remain in the female role and resigned to a life of isolation. Cases of this type are often discovered during the third, fourth, or fifth decade because of some incidental disease, perhaps a hernia. Thirdly, the patient may develop a powerful libido of the feminine type, often marrying and attempting frequent intercourse as the female partner despite the unsuitability of the genitalia (Young, 1937; Rubovits and Saphir, 1938; Crossen, 1939; Witschi and Mengert, 1942). Castration results in a considerable diminution of the libido.

It seems likely that the environment is one of the most important factors in the development of sexual inclinations, and if the child is reared as a boy from an early age one need not be too fearful of creating a practising homosexual. The advice given regarding these cases will therefore depend very largely upon the age at which it is sought: once the adolescent patient has established a conscious sexual orientation it is seldom wise to reverse it, and a change of sex in a case brought up as a girl should be made only at the patient's request. In those choosing to remain as females, the adaptation of anatomy and appearance can never be entirely satisfactory, but castration and amputation of the penis, followed by intermittent stilboestrol therapy, is probably the correct treatment. If, on the other hand, an opinion is requested in the case of a young child, it will be safer to advise rearing as a boy, even if this necessitates a change of sex, which may be accomplished at this stage without too great an upheaval.

Case 3

This child (Mr. Twistington Higgins's case) was brought to the hospital at the age of 23 months, the parents having been advised that its sex could not be determined before the age of 3 years. The father believed that the child behaved more like a boy; the mother was too distressed to have a coherent opinion.

FIG. 5.—Intersex male—Case 3. Photograph of the external genitalia.

The child was normally grown for his age, the penis well formed but with marked chordee, and there was a single wide meatus in the perineum. No gonads were palpable (see Fig. 5). At urethroscopy no verumontanum was seen, but there were two duct orifices at the expected level. In the region of the perineal membrane there was a small vaginal orifice into which only the tip of a ureteric catheter could be passed. Bimanual examination revealed a firm cord-like structure extending upwards from the region of the urethra to the left side of the pelvis. At laparotomy there was a small uterus pulled well over to the left, with uterine tubes on either side and prominent round ligaments (see Fig. 6). No gonad could be found on the left; on the

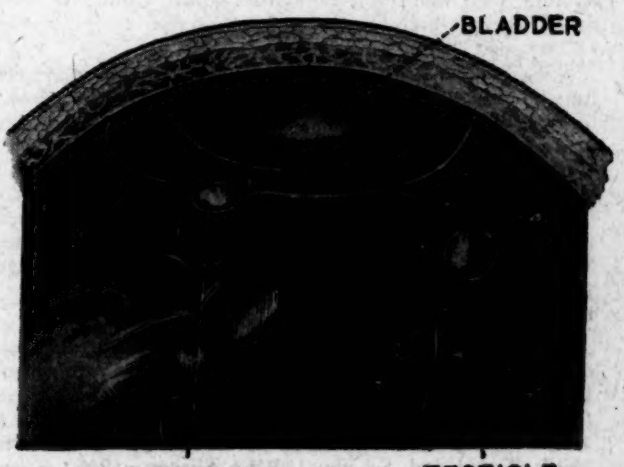

FIG. 6.—Diagrammatic drawing of the view at laparotomy.

right there was a testicle (confirmed histologically) in the normal position of the ovary. 17-Ketosteroid excretion was 1.2 mg. per 24 hours. The child will be brought up as a boy and the hypospadias deformity repaired.

In another very similar case the single gonad had the macroscopic appearance of an ovary and was actually removed on this supposition. Histologically, however, the organ proved to be a testicle. It is advisable, therefore, to identify the type of gonad by biopsy before undertaking definitive treatment.

Case 4

This child (Mr. Twistington Higgins's case) was brought to hospital at the age of 6 because of abnormalities of the penis. He had been reared as a boy and had all the habits of his kind. On examination there was an extremely small phallus with a perineal urethral meatus and poorly developed labioscrotal folds (see Fig. 7). Two minute bodies could, however, be felt in the inguinal regions. On urethroscopy there was no verumontanum, though two minute ducts opened at the expected position. A large vagina was found with an orifice at the level of the perineal membrane, but a careful search revealed no evidence of a cervix. A cord-like structure extending upwards from the urethra was palpated per rectum. The blind vaginal pouch and the presence of gonads in both groins confirmed the clinical impression of masculinity. Growth of the penis was stimulated by implantation of testosterone, and reconstruction of the penile urethra was embarked upon.

FIG. 7.—Intersex male—Case 4. Photograph of the external genitalia.

Case 5

The child (Mr. Twistington Higgins's case) attended hospital at the age of 8 years, having been brought up as a girl. There was a small but well-formed penis with perineal hypospadias and marked chordee. Both testicles could be palpated in the inguinal regions, but the skin over them was smooth and in no way suggested the formation of a scrotum. A well-formed vaginal pouch could be seen behind the urethral meatus. 17-Ketosteroid excretion was 1.4 mg. per 24 hours.

A laparotomy was performed and female organs were not found. The hypospadias was repaired by the Denis Browne method, leaving the vaginal pouch untouched. The child was extremely pleased with the sex reversal, and when reviewed three years later had adapted himself admirably to the new role. Micturition was normal, although endoscopy revealed a very wide orifice into the vaginal pouch, the urethra being found only with difficulty. This case has been illustrated elsewhere (Higgins, Williams, and Nash, 1951).

True Hermaphrodites

True hermaphrodites—that is, individuals possessing both testicular and ovarian tissues—are now reported with a regularity which indicates a condition of no exceptional rarity (Young, 1937; Doss and Priestley, 1940; McIver, Seabaugh, and Mangels, 1944; McKenna and Kiefer, 1944; Moriarty, 1944; Davis and Scheffey, 1946; Stirling, 1946; Engel, Yeaw, and Lattimer, 1946; De Moura and Basto, 1946; Weed *et al.*, 1947; Patton, 1948; Wilkins, 1950; Fergusson, 1951; Capon, 1951). Over 40 histologically verified cases are known, and there are many others in which this diagnosis is probable but unproved. The possibility is therefore one to be considered in any case displaying external genitalia of equivocal sexuality, and the desirability of diagnosis during childhood is emphasized by the frequent coincidence at puberty of signs indicative of both testicular and ovarian function.

The gonads of the true hermaphrodites may be unmistakable testicles or ovaries on the same or opposite sides, but more often tissue histologically characteristic of either is contained within a single body. Ovo-testes may be bilateral or one may be associated with a normal contralateral gonad. The two portions of an ovo-testis may be macroscopically distinguishable, as in the case reported below and that described by Doss and Priestley (1940), so that surgical separation is possible, but in a greater number it is only the histology which reveals the true nature of the organ. At times gonadal tissue is found in bodies which may not be recognized at operation as gonads at all; a thickened area on the broad ligament beneath the Fallopian tube may prove to contain either testicular or ovarian tissue. The ovo-testis appears to have the same tendency to descend into the scrotum as the normal testis, but a gonad containing ovarian tissue alone does not descend beyond the inguinal canal unless in a hernia. Graafian follicles and corpora lutea are commonly to be found in the ovary; spermatogenesis is less often complete, though a few motile sperms have been recovered from ejaculates in some instances. No known case has achieved parenthood in either role.

Some sort of uterus has been present in most cases, a vagina in almost every one in which a search has been made. The latter may open externally, into the posterior urethra, at the level of the perineal membrane, or occasionally, perhaps, at the verumontanum.

The external appearance of the genitalia in the true hermaphrodites is very variable; it presents no diagnostic feature, and a catalogue of the frequency with which the various patterns have been recorded is of little value. A phallus of moderate size is the rule, with a urethral meatus in the position of perineal hypospadias. Nevertheless a penis of normal appearance with a terminal meatus has been described in three cases. The scrotum may be bifid and its halves may resemble labia majora. It may or may not contain gonads. The bodily form is sometimes indifferent, but one sexual type is more often predominant, though not always the type appropriate to the appearance of the genitalia. The psychological orientation corresponds so closely to the upbringing that the importance of environment as the determining factor can scarcely be doubted. The majority of cases have been sexually univalent; many have married and enjoyed satisfactory intercourse only in the role in which their education has led them to expect satisfaction.

The diagnosis of true hermaphroditism can be made only by gonadal biopsy, and in view of the importance of recognizing the condition this measure should not be omitted in any suspicious case. The sexual category in which the patient is to live will normally be determined by that already chosen, and only where the emotions are in serious conflict with the accepted role will any change be considered (Stromme, 1948). Treatment endeavours to approximate the bodily form and the appearance of the genitalia to the chosen role, and must clearly be directed both towards the gonads and towards the secondary sexual organs. The "male" cases require repair of hypospadias and hysterectomy; the "female," amputation of the phallus and perhaps plastic operations on the vagina. But if ovarian tissue is allowed to remain in the "male," enlargement of the breasts is to be expected at puberty, while "females" with testicular cells are apt to grow beards and have deep voices. The latter manifestations may be prevented by the removal of the unwanted gonad where this is present as a distinct

organ, but with the ovo-testis distinction is seldom possible, and the choice must be made between castration and the possibility of inappropriate developments at puberty.

Case 6

This child (Mr. Denis Browne's case) first attended hospital at the age of 3. He had always been regarded as a boy, and no doubts were felt about his sex. There was a penile hypospadias; the right testicle was palpable in the scrotum accompanied by a hernia; the left testicle was not felt. A first-stage operation for hypospadias was performed at the age of 6. The child then lost touch with the hospital during the war, and the second stage was not completed until seven years later. The left testicle was still not palpable. After a further year, at the age of 14, swelling of both breasts was noticed and gradually became more prominent. An endocrinological opinion was sought, and Dr. Alex Russell suggested that he might be suffering from male hypogonadism (Klinefelter syndrome), but an estimation of excretion of follicle-stimulating hormone (carried out by Dr. Swyer, of University College Hospital) gave a normal result (5 mouse units) and failed to confirm this diagnosis. 17-Ketosteroid secretion was 5.2 mg. per 24 hours. He was then given a course of "antuitrin S" (chorionic gonadotrophin) in the hope of stimulating the descent of the left testicle, but as his only response to this treatment was increasing size of the breasts the possibility of intersex had to be seriously considered.

FIG. 8.—True hermaphrodite — Case 6. Photograph of the external genitalia after the repair of hypospadias.

When seen at the age of 15 he was somewhat undersized, but in general of boyish appearance. His attitude appeared to be entirely male, and he entered fully into the activities of his male contemporaries. The voice, however, was high-pitched and the breasts were large, resembling those of an adolescent girl. As shown in Fig. 8, there was a well-formed phallus, and the hypospadias operations had been successful in producing a terminal meatus. A gonad was palpable on the right side of the scrotum, none on the left. Urethroscopy demonstrated the absence of a verumontanum, though one small duct orifice was present in the posterior urethra a short distance below the bladder neck. Lower down, at the level of the perineal membrane, the vaginal orifice was identified and a catheter was passed into it. A vaginogram showed a capacious organ drawn over to the right side of the pelvis, and the dye appeared to have entered the uterus. At operation he proved to have a uterus and tubes, with a cystic left ovary: the gonad in the scrotum was an ovo-testis, and was accompanied by both a Fallopian tube and a vas deferens. Hysterectomy was performed; the ovary and ovarian half of the ovo-testis were removed and the breasts amputated. He continues as a boy.

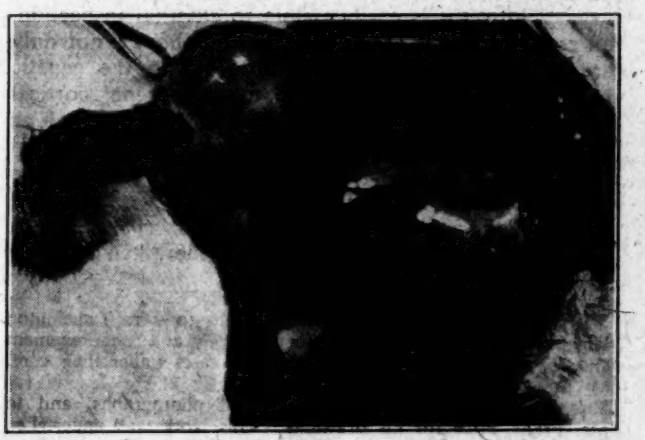

FIG. 9.—Case 6. Showing the pelvic cavity at laparotomy.

Gonadal Tumours in the Intersexes

The presence of a neoplasm in the gonad of intersex cases has been reported on a number of occasions, and, since the original gonad may be destroyed, proper classification of these instances is not always possible. Tubular adenomata and malignant disease are well-known complications of undescended testicles, and occur in intersex patients (Metcalfe, 1930). In intersex females, dysgerminoma of the ovaries has been recorded (Long, Ziskind, and Storck, 1941; Corriden, 1949), though it is difficult to rule out the possibility of a seminoma in an ovo-testis in such a case. The history in the case of the teratoma reported by McCrea (1930) as occurring in a "male pseudohermaphrodite" undoubtedly suggests a true hermaphrodite.

Summary: Differential Diagnosis

All children in whom the genitalia are of equivocal sexuality require a careful investigation before any treatment is embarked upon. Cases of hypospadias

Common Findings in the Various Types of Intersexuality

Type	General	Breast Development	Menstruation	Externally Palpable Gonads	Rectal Examination	Endoscopy	Remarks
A. Intersex females:							
1. Hormonal: Adrenal sex reversal	Precocity and virilization of female bodily form	Very rare	Very rare	Absent	Mobile uterus, supple vagina	Vagina with normal cervix	Diagnosis from combination of anatomy and endocrine disturbance
2. Non-hormonal: With urinary obstruction. ? others	Female body	Present	Present	,,	?	?	Exploration required
B. Intersex males:							
1. With purely feminine external genitalia	Adolescent female development	Adolescent	Absent	Present	Nil	Female urethra; blind vagina	Exploration may be required for confirmation of diagnosis
2. With masculine external genitalia but feminine uterus	Normal male	Absent	,,	,,	?	?	Only likely to be discovered at operation
3. With external genitalia of equivocal sexuality	Normal male or hypogonad changes	Usually absent. Present in hypogonad cases	,,	Sometimes absent	Prostate or fibrous vaginal cord	Verumontanum or vagina; abnormal uterine cervix rarely	Laparotomy and biopsy required except where a normal verumontanum is found on urethroscopy
C. True hermaphrodites ..	Variable	Usually present	Usually present	Usually present	Variable, usually a vagina	Variable, usually a vagina with cervix	Laparotomy and gonadal biopsy essential

should always be suspect unless both testicles can be palpated with certainty, but in the great majority a urethroscopy will reveal a normal verumontanum and render unnecessary any more extensive exploration. Diagnosis without laparotomy may also be possible where the combination of anatomy and endocrine disorder points to the hormonal type of intersex female. The accompanying table sets out the common findings in the other types described in this paper.

The most difficult problem is provided by the newborn infant whose genitalia are of equivocal sexuality; the anatomy of the genital passages of all three main groups may be identical and, except in the cortin-deficiency cases, adrenal abnormalities may not at this stage be manifest. The urethral orifice is fortunately wide enough to admit a urethroscope at a very early age in these cases, but there will remain a few in which only a laparotomy can establish the diagnosis. Nevertheless, it should be clear from the present review that, unless the vaginal introitus is easily visible to external inspection, all equivocal cases are better reared as boys; not only are intersex males more common, but in the genetic females masculinization is due to the adrenal cortical secretions, the androgenic influence of which is such as to render them happier in the male role. Only in exceptionally rare cases, therefore, should it be impossible to give a confident opinion during the first weeks of life, and with the advance of paediatric surgery the age at which laparotomy may be safely undertaken is being rapidly reduced.

I should like to express my gratitude to Mr. Twistington Higgins and Mr. Denis Browne for their help and encouragement and for permission to publish details of cases under their care. My thanks are also due to Mr. Derek Martin, of the Hospital for Sick Children, for his excellent clinical photographs, and to Mr. Frank Price for his drawings. This work was undertaken during the tenure of the Leverhulme Research Scholarship of the Royal College of Surgeons, and I must acknowledge the kindness of the College authorities in allowing me to reproduce drawings of specimens preserved in the museum.

REFERENCES

Bleyer, L. F. (1948). *Amer. J. Surg.*, 76, 448.
Browne, D. (1950). In *Techniques in British Surgery*, edited by R. H. Maingot. Saunders, Philadelphia and London.
Capon, A. W. (1951). *Lancet*, 1, 563.
Carlisle, W. T., and Geiger, C. J. (1938). *Amer. J. Obstet. Gynec.*, 36, 1047.
Chanis, D. (1942). *J. Urol.*, 47, 508.
Cook, J. (1950). *Brit. J. Urol.*, 22, 211.
Corriden, T. F. (1949). *New Engl. J. Med.*, 240, 247.
Coste, G. (1947). *J. Mt Sinai Hosp.*, 14, 170.
Crossen, H. S. (1939). *Amer. J. Obstet. Gynec.*, 38, 123.
Davis, D. M., and Scheffey, L. C. (1946). *J. Urol.*, 56, 715.
De Moura, A. C., and Basto, L. P. (1946). Ibid., 56, 725.
Doss, A. K., and Priestley, J. T. (1940). Ibid., 43, 859.
Engel, E. T., Yeaw, R. C., and Lattimer, J. K. (1946). Ibid., 56, 731.
Everidge, J. (1945). *Proc. roy. Soc. Med.*, 38, 649.
Fazen, L. E. (1949). *Wis. med. J.*, 48, 1077.
Fergusson, J. D. (1951). *Brit. J. Urol.*, 23, 29.
Genitis, V. E., Bronstein, I. P. (1942). *J. Amer. med. Ass.*, 119, 704.
Goldberg, M. B., and Maxwell, A. F. (1948). *J. clin. Endocrinol.*, 8, 367.
Greenhill, J. P., and Schmitz, H. E. (1940). *West. J. Surg.*, 48, 36.
Hain, A. M., and Schofield, J. E. (1947). *J. Obstet. Gynaec. Brit. Emp.*, 54, 97.
Hamblen, E. C., Carter, F. B., Wortham, J. T., and Zanartu, J. (1951). *Amer. J. Obstet. Gynec.*, 61, 1.
Harris, C. F., and Scowen, E. F. (1951). *Arch. Dis. Childh.*, 26, 423.
Healey, C. E., and Guy, C. C. (1931). *Arch. Path.*, 12, 543.
Higgins, T. T., Williams, D. I., and Nash, D. F. F. (1951). *The Urology of Childhood*. Butterworth, London.
Hinman, F. (1951). *J. clin. Endocrinol.*, 11, 477.
Howard, F. S., and Hinman, F. (1951). *J. Urol.*, 65, 439.
Ingersoll, F. M., and Finesinger, J. E. (1947). *Surg. Clin. N. Amer.*, 27, 1218.
Jolly, H. R. (1951). *Proc. roy. Soc. Med.*, 44, 459.
Keen, J. A., and de Villiers, D. P. (1949). *S. Afr. med. J.*, 23, 172.
Kozoll, D. D. (1942). *Arch. Surg.*, 45, 578.
Krückmann, I. (1937). *Virchows Arch. path. Anat.*, 298, 619.
Long, C. H., Ziskind, J., and Storck, A. H. (1941). *Surg. Gynec. Obstet.*, 73, 811.
McCrea, E. D'A. (1930). *Brit. J. Surg.*, 18, 91.
McIver, R. B., Seabaugh, D. R., and Mangels, M. (1944). *J. Urol.*, 52, 67.
McKenna, C. M., and Kiefer, J. H. (1944). Ibid., 52, 464.
McMillan, W. M. (1942). *Ann. Surg.*, 116, 266.
Metcalfe, R. H. (1930). *Brit. J. Surg.*, 18, 335.
Moriarty, J. D. (1944). *Amer. J. Path.*, 20, 799.
Nilson, O. (1939). *Acta chir. scand.*, 83, 231.
Novak, J. (1943). *Amer. J. Obstet. Gynec.*, 45, 856.
Oberthur, H. (1950). *Mém. Acad. Chir., Paris*, 76, 258.
Panos, T. C. (1950). *Pediatrics*, 5, 972.
Patton, W. H. G. (1948). *Anat. Rec.*, 101, 479.
Pratt, J. P. (1940). *Amer. J. Obstet. Gynec.*, 40, 870.
Rubovits, W. H., and Saphir, W. (1938). *J. Amer. med. Ass.*, 110, 1823.
Siak, I. R., and Cornwell, P. M. (1942). *J. Urol.*, 47, 721.
Stirling, W. C. (1946). Ibid., 56, 720.
Stollmeyer, J. E. C., and Latour, J. P. A. (1950). *Canad. med. Ass. J.*, 63, 494.
Stromme, W. B. (1948). *Amer. J. Obstet. Gynec.*, 55, 1060.
Von Gierke, E. (1928). *Verh. dtsch. path. Ges.*, 23, 449.
Wachstein, M., and Scorza, A. (1951). *Amer. J. clin. Path.*, 21, 10.
Ward-McQuaid, J. N., and Lennon, G. G. (1950). *Surg. Gynec. Obstet.*, 90, 96.
Weed, J. C., Segaloff, A., Weiner, W. B., and Douglas, J. W. (1947). *J. clin. Endocrinol.*, 7, 741.
Weisman, A. I., and Schwarz, A. (1941). *J. Amer. med. Ass.*, 117, 2248.
Wilhelm, S. F. (1947). *J. Mt Sinai Hosp.*, 14, 679.
Wilkins, L. (1950). *Endocrine Disorders of Childhood and Adolescence*. Springfield, Illinois.
—— Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Rosemberg, E., and Migeon, C. J. (1951). *J. clin. Endocrinol.*, 11, 1.
Witschi, E., and Mengert, W. F. (1942). Ibid., 2, 279.
Young, H. H. (1937). *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*. Williams & Wilkins, Baltimore.

AGRANULOCYTOSIS CAUSED BY AMIDOPYRINE

AN AVOIDABLE CAUSE OF DEATH*

BY

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Some years ago within a month I saw three necropsies on patients who had died of agranulocytosis. They were all males, patients of one surgeon, and, as they had all received full doses of sulphapyridine, the agranulocytosis was ascribed to this drug. Because there had been no similar cases in the rest of the hospital, I studied the matter further, and found that all three had received full but not excessive doses of either "cibalgin" or "veramon" during the weeks preceding death. I did not know these preparations, but Martindale's *Extra Pharmacopoiea* informed me that they were amidopyrine–barbiturate mixtures. It seemed more reasonable to assume that the amidopyrine had caused the agranulocytosis.

I was surprised to find that neither the surgeon, his registrar, nor his house-officer had realized that cibalgin and veramon contained amidopyrine. I was therefore not particularly surprised when other clinical pathologists told me of similar tragedies, or when I found it re-enacted in my own hospital.

Case Report

A woman aged 67 had had osteoarthritis of several joints, a duodenal ulcer, and early cardiac decompensation. In 1948 she was operated on for a strangulated hernia. On August 22, 1950, she developed a sore throat, which got worse until August 26, when she was referred to hospital and treated as an out-patient with penicillin and tab. codein. co.; she improved and was discharged on August 29. On September 6 she was again sent to hospital, very ill, prostrated, pale, dyspnoeic at rest, febrile, with a temperature of 101.4° F. (38.6° C.), a pulse of 125, and a very dry tongue. A diagnosis of bleeding from her duodenal ulcer was made, and she was admitted. (Hb, 8.9 g./100 ml.; blood urea, 76 mg./100 ml.; serum chloride, 84 mEq./litre; thymol turbidity, 5.5 units; flocculation positive.) Transfusion of 1,500 ml. of blood had little effect. On September 7 the white blood cells numbered 3,500 per c.mm., all lymphocytes. Treatment was ineffective, and she died that evening. Necropsy showed one ulcer and several superficial erosions in the pharynx, and a large pyloric ulcer, without

*Based on a paper read before the Association of Clinical Pathologists in January, 1951.

any evidence of recent bleeding. Sections of the bone marrow showed that all granulocytes had disappeared, and only plasma cells and a few erythroblasts could be seen.

The diagnosis of agranulocytosis having been established, her relatives were questioned, and they reported that she had taken "allonal" tablets. The patient's practitioner confirmed that she had prescribed at least six allonal tablets and probably more over a period. The practitioner did not know that allonal contained amidopyrine.

The patient presented a difficult diagnostic problem. The prostration, dehydration, and raised blood urea suggested bleeding from the peptic ulcer which was known to be present, but the fever and sore throat are not typical of bleeding. Pharyngeal ulceration was not present at the time of admission. The diagnosis of agranulocytosis was, in fact, made only after a blood count had demonstrated it, too late to benefit the patient. Now that antibiotics are widely used it seems probable that such atypical cases may become more frequent.

Preparations Containing Amidopyrine

Between 1934 and 1937 much publicity was given to the occurrence of agranulocytosis in subjects taking a patent medicine containing amidopyrine. Most practitioners believe that because of this publicity amidopyrine was removed from the proprietary medicines which had previously contained it. In fact, the only restriction imposed was to include amidopyrine in Schedule IV of the Pharmacy and Poisons Act, 1933, thus making it illegal to sell or distribute it or its mixtures except on the prescription of a registered practitioner. The patent medicines advertised direct to the public were either withdrawn or their composition was altered; but the ethical preparations which contained amidopyrine and were distributed under a proprietary name remained available to any practitioner, and can still be prescribed under their proprietary names. Some years ago Dr. E. N. Davey found 29 such mixtures available as tablets; most of these have disappeared, but there are still 10 makes of tablets which contain amidopyrine and are distributed under a proprietary name. These are: allonal* (Roche Products), amidophen (Eli Lilly), amytal compound (Eli Lilly), cibalgin (Ciba), corosedine (Bengue), optalidon (Sandoz), somnosal (Napp), taumasthman (Wallace), veramon (British Schering), and veropyron (Gedeon Richter).

There is also a preparation intended for parenteral use—irgapyrin (Geigy); this is unlikely to be dangerous, because the injections will be given by the practitioner, and the presence of amidopyrine is clearly stated on the containers and leaflets.

Amidopyrine causes agranulocytosis in Great Britain to-day only when it is ordered as a mixture under a proprietary name by a practitioner who does not realize he is prescribing amidopyrine. The danger is simply that the practitioner rarely dispenses these mixtures himself, and easily forgets their composition once he has tried them and found them potent.

Incidence of Agranulocytosis

Most estimates of the incidence of agranulocytosis are guesswork. Recently 19 series totalling 3,344 patients who received parenteral amidopyrine were collected for me in Switzerland; of these, only four developed agranulocytosis, but many had received the drug for only a few days. Avery Jones (1947), in his Goulstonian Lectures, pointed out how such collected series or mass hospital statistics may be highly fallacious.

I have found three published experiments, and have private information of a fourth, in which amidopyrine was administered to a series of 200 or more patients for considerable periods—nearly all over 14 days, some over a year—under conditions such that agranulocytosis would have been recognized had it occurred (see Table).

Author	Route	Patients at Risk	Agranulocytosis		Deaths
			Cases	%	
Holten (1934)	Oral	352	5	1·42	5
Rawls (1936)	,,	400	4	1·00	3
Gsell and Mueller (1950)	Parenteral	220	2	0·91	0
Cermák (1951)	Oral	300	0	0	0
Total		1,272	11	0·86	8

An incidence of 0.86% is so high that it seems barely credible, but, so far as I can judge, this is the best estimate yet available. It is possible that Cermák's experience represents a real difference in incidence, but one must remember that, were the true incidence of agranulocytosis 1%, there is 1 chance in 20 that no cases would occur in a series of 300 patients at risk.

Nevertheless, many practitioners knowingly use amidopyrine regularly, claiming that it and its mixtures with barbiturates are more potent than any other analgesic except opiates. They point out that amidopyrine is sold without restriction in France, Belgium, Germany, and Switzerland, deducing that it cannot be so very dangerous, and suggest that the fears expressed in Denmark, Great Britain, and the United States are exaggerated.

Those interested in the marketing of amidopyrine make other suggestions: that agranulocytosis is caused by impurities in some batches of amidopyrine (a possibility of little significance to the practising physician); or that the barbiturate of the mixture is the cause of agranulocytosis, ignoring the clear incrimination of the amidopyrine component by Madison and Squier (1934), Plum (1934, 1937), Israëls and Wilkinson (1937), and others, who produced severe leucopenia with fever and prostration by giving 0.2–0.5 g. of amidopyrine to patients convalescent or recovered from amidopyrine agranulocytosis.

It has also been suggested that agranulocytosis occurs only in patients whose bone marrow has been damaged by chronic infection. This may be true, but it does not help the practising physician. Infection is a common cause of pain, and an analgesic which damaged the marrow of infected patients only would be just as unacceptable as one which damaged normal marrow. A last suggestion is that the Anglo-Saxons form a racial group particularly susceptible to agranulocytosis. If we ignore the difficulty of defining an Anglo-Saxon, this hypothesis is quite attractive, and it is not difficult to assemble evidence to support it.

Personal communications from Professors Brüll, Govaerts, and Roskam, in Belgium, reveal that they have seen no cases of agranulocytosis attributable to amidopyrine during the past year or two, although amidopyrine mixtures are commonly used.

Dr. L. Cermák, of Prague, writes: "Amidopyrine is a drug very commonly used in Czechoslovakia, and up to the last few months it could be obtained without a prescription . . . so far as I could ascertain from the archives of the clinic, the occurrence of agranulocytosis as a clinical entity is negligible. In five years only four cases have been treated . . . I have studied the case histories of about 2,000 patients . . . from this point of view. The average amount of amidopyrine administered to one patient with chronic polyarthritis in the course of one year was over 1,000 g. Among all 300 patients I did not find one case of agranulocytosis."

Such clear-cut statements are difficult to explain away. It is unlikely that typical cases are missed, and sampling errors are not likely to be of significance. Taken together with the statement of one manufacturer, whose preparation is very popular in France and Switzerland, that no case of agranulocytosis following its use had ever been reported

*Since this paper was written Roche Products have announced that as from May 1, 1952, the amidopyrine in allonal would be replaced by *iso*propyl phenazone (*Pharmaceutical Journal*, May 3, p. 312). From now on, therefore, allonal is unlikely to be a cause of agranulocytosis, for *iso*propyl phenazone does not, so far as is known, cause agranulocytosis.

to him, it seems very reasonable to consider whether there may be a significant geographical or racial variation in susceptibility to amidopyrine.

Nevertheless, Dr. Konrad Müller, of Westphalia, a physician, has seen four cases during the past four or five years—that is, as many cases as I have seen in 10 or 11 years, even though I have been a clinical pathologist serving 5 to 10 consultant physicians and a number of general practitioners. Rohr (1939) observed 16 cases in his clinic at Zurich between 1918 and 1939, and concludes that amidopyrine should be available only on prescription.

In 1931 Kracke observed that agranulocytosis was commoner in doctors, their wives, and in nurses than in other groups of the community, and attributed it to their greater use of benzamine compounds, derived from aniline; and in 1934 Kracke and Parker noted the low incidence in Great Britain, and hinted that the incidence was low because benzamine compounds were little used. The statistics available are incomplete and peculiar. They become somewhat less obscure when they are converted into cases per million inhabitants of the area considered; an incidence of one per million would be equivalent to about 45 cases in Great Britain.

Kracke and Parker's figures give, as total cases reported from all causes per million inhabitants: Germany 5, U.S.A. 3.5, France 2.5, Great Britain 0.12. Plum (1937), covering cases due to amidopyrine reported during the four years 1933–6, gives an annual incidence per million of U.S.A. 0.25, Germany 0.03, Great Britain 0.07, Switzerland 0.3, Sweden 0.46, and Denmark 2.9; if unpublished cases are added the Danish incidence swells to 4.8. If one assumes that Rohr's cases were all drawn from the canton of Zurich, the annual incidence is 1.3 per million. These figures appear fantastic. Denmark, Sweden, and Switzerland had at that time no restriction on the use of amidopyrine. Can the Danes be six times more susceptible than the Swedes, or can they have used six times as much amidopyrine?

A reasonable explanation can be offered by the observations of Plum (1937) and Dameshek and Colmes (1936). Plum suggests that one case is reported for every 65–70 kg. of amidopyrine imported into Denmark, while Dameshek and Colmes estimate one case for every 10,000 prescriptions; these estimates agree quite satisfactorily. Plum quotes cases in which the patient's medicine chest contained several packages of different proprietary medicines containing amidopyrine, and concludes: "It is extraordinarily difficult to obtain reliable anamnestic data . . . in several cases it has been necessary to investigate the stock of drugs on hand in the patient's home with the painstaking exactness of a detective, even though the relatives insisted that it would be useless to look." The Danish figures are high simply because Plum did work with the painstaking accuracy of a detective; and Rohr has high figures for Zurich because he is a haematologist of international repute to whom many of the recognized cases are referred. It seems probable that the incidence of agranulocytosis in a community which can buy amidopyrine freely must be of the order of two to five cases annually per million population, equivalent to 90 to 225 cases in Great Britain—at least, this appears to be reasonable for countries north and west of Czechoslovakia.

There is one observation which suggests that this estimate is too low. Stenbeck (1935, cited by Plum) introduced amidopyrine into his practice, and in the next six years observed 10 cases of agranulocytosis, which had previously been unknown. Even if we assume an improbably large practice of 10,000 souls, this is an incidence of about 150 cases annually per million inhabitants.

The Mechanism of Agranulocytosis

The direct toxicity of amidopyrine is negligible. Dameshek and Colmes stated that patients who have recovered from agranulocytosis caused by amidopyrine show no skin sensitivity to the drug, but show skin sensitivity to a solution of amidopyrine in serum which has been allowed to stand for several days. In those skin-sensitive patients in whom it was tried, ingestion of amidopyrine caused leucopenia. Agranulocytosis therefore seems to be an allergic manifestation, requiring initial sensitization, followed after weeks, months, or even years by re-exposure to the drug. Since individuals vary greatly in their capacity to become sensitized to synthetic chemicals, there is bound to be great variation in the duration of the exposure to the drug before sensitization actually occurs.

Sensitization, and therefore agranulocytosis, will occur so long as amidopyrine is used. Most practitioners refuse to prescribe amidopyrine under its own name because they realize its danger—as a result, Bayer's original brand, "pyramidon," has been taken off the British market because the demand for it is negligible. Sensitization and agranulocytosis are being caused to-day by one or other of the 10 preparations listed above; and these preparations are often (but not always) prescribed in ignorance of the fact that they contain amidopyrine.

Substitutes for Amidopyrine

The excellence of amidopyrine–barbiturate mixtures as pain killers seems to depend on the combination of a peripheral vasodilator with a central sedative. There is no obvious reason why the dangerous amidopyrine should not be replaced by a less dangerous drug with similar pharmacological properties, such as acetylsalicylic acid, phenacetin, salicylamide, or mixtures thereof; and at least one firm has already issued such a mixture and requested its representatives to advocate its use in preference to their amidopyrine–barbiturate mixtures. It would undoubtedly be claimed that such mixtures were less effective than those containing amidopyrine, but now that Asher (1948) has shown how to compare the efficiency of analgesics it should be possible to settle this question by arranging a large-scale trial of the two types of mixture. Since any such trial would expose several hundred patients to the risk of agranulocytosis, it may be that it would be considered unjustifiable, but it might well save future generations all over the world from the risk of agranulocytosis, and I think such trials should be conducted.

Discussion

Such is the situation of amidopyrine. Its dangerous effects were well known 15 years ago, when Sir William Willcox found that as a component of a patent medicine it had killed a number of people. Is it possible to reduce its toll still further?

Before rushing to advise remedies for this specific case, it is well to consider whether it is unique; for, if it is not, remedies for other dangers should be considered at the same time.

Amidopyrine is not unique. A hypnotic, "sedormid," causes purpura, sometimes fatal, in patients who have been sensitized to it; Ackroyd (1949a, 1949b, 1949c) has demonstrated the mechanism of the purpura—a direct thrombocytolysis by the drug. Cryogénine (phenylsemicarbazide) is an antipyretic popular in France, and spasmodic attempts to introduce it into this country have been made. It causes haemolytic anaemia, and in March, 1950, Dr. Debré complained to the Academy of Medicine that during the previous year at the Enfants-malades he had seen six cases of haemolytic anaemia in children caused by it (Debré *et al.*, 1950). The cryogénine had been administered in suppositories advertised direct to the public under the name *Défébryl-enfants*. Buisine and Vincent (1950) reported a similar case in a child suffering from rubella complicated by agranulocytosis caused by the concurrent administration of "erythra"—a preparation of amidopyrine. Cryogénine is not on any poisons list in this country.

Clinical and forensic pathologists see too many tragedies due to drug idiosyncrasy. The Poisons Board is charged with the duty of making regulations to control the use of

such drugs, and when provided with evidence does so: but there is a lamentable lack of contact between clinical pathologists and the Poisons Board. I believe that there is a need for a small standing committee of clinical and forensic pathologists, whose terms of reference should be: "To collect evidence on the production of injurious effects by drugs administered for therapeutic purposes; to deduce from this, and any other evidence available, whether the therapeutic value of any such drug is great enough to warrant its continued use; and to submit representations and recommendations to the Poisons Board on the regulations for the manufacture, sale, advertising, packaging, labelling, or prescription of drugs which have been shown to produce injurious effects."

The Association of Clinical Pathologists has many forensic pathologists as members; if the association formed a committee, evidence could be obtained without excessive formality, but the committee would have no official status. Alternatively, a committee could be set up by the Central Health Services Council, with the advantage of having statutory justification. Probably maximum efficiency would be attained if the A.C.P. set up a small committee to collect evidence, and if the Central Health Services Council also set up its committee, to which the members of that formed by the A.C.P. were co-opted.

In the specific case of amidopyrine it is clear that the present regulations for Schedule IV are inadequate. Various rules have been made in different countries, all of which would have some disadvantage in England. I suggest that the Poisons Board should introduce a new regulation to the effect that "no prescription for amidopyrine, its salts, or mixtures of these with any other substance shall be valid unless the prescriber states specifically on the prescription that amidopyrine is required." The prescription for, say, veropyron could then read "amidopyrine mixture, veropyron," or "amidopyrine-barbiturate mixture, veropyron." Such a rule would ensure that no practitioner could remain in ignorance of the danger of the mixture he was prescribing, but it would in no way interfere with his responsibility or his right to order any preparation which, in his opinion, was necessary for the patient; nor would it interfere with the existing proprietary mixtures.

Summary

A case of agranulocytosis caused by amidopyrine is described.

It is shown that the best available evidence suggests that if this drug is administered regularly to a series of patients agranulocytosis will occur in about 0.8%.

It causes agranulocytosis in Great Britain when an amidopyrine mixture is prescribed under a proprietary name by a practitioner who does not know that it contains amidopyrine.

It is shown that, among a population which can obtain amidopyrine freely, an annual incidence of agranulocytosis between 2 and 5 per million may occur, and that if its use is encouraged the incidence may increase many times.

Possible substitutes for amidopyrine in mixtures are suggested.

Attention is drawn to other drugs with undesirable side-reactions. It is suggested that a standing committee of clinical and forensic pathologists should collect evidence on drugs causing injurious side-effects and submit their conclusions to the Poisons Board.

It is suggested that no prescription for a mixture containing amidopyrine should be valid unless the word amidopyrine appears on the prescription.

I am indebted to my colleagues in other countries who have so kindly and precisely replied to my inquiries; their names are given in the text. Summaries of the restrictions under which amidopyrine is prescribed in Norway and Sweden were given by the Norwegian and Swedish Ministries of Health, and Dr. Torben K. With obtained the Danish regulations for me. The Ministry of Health of the Czechoslovakian Republic and the Czechoslovak Medical Society enabled me to correspond with Dr. L. Cermák: to all these I am indebted. I have been greatly assisted by the directors and medical advisers of several pharmaceutical manufacturing houses who have obtained unpublished observations and placed them freely at my disposal, and spared no trouble to ensure that this review is as truthful as possible. It is with regret that, at their own request, I do not mention them by name.

References

Ackroyd, J. F. (1949a). *Clin. Sci.*, **7**, 249.
—— (1949b). Ibid., **8**, 235.
—— (1949c). Ibid., **8**, 269.
Asher, R. (1948). *Lancet*, **2**, 771.
Buisine, A., and Vincent, J. (1950). *Ann. Biol. clin.*, **8**, 326.
Cermák, L. (1951). Personal communication.
Dameshek, W., and Colmes, A. (1936). *J. clin. Invest.*, **15**, 85.
Debré, R., Lamy, M., Mozziconacci, P., Aussanaire, M., and Buhot, S. (1950). *Bull. Acad. nat. Méd., Paris*, **134**, 225.
Gsell, O., and Mueller, W. (1950). *Schweiz. med. Wschr.*, **80**, 310.
Holten, C. (1934). *Nord. med. T.*, **8**, 1659.
Israëls, M. C. G., and Wilkinson, J. F. (1937). *Quart. J. Med.*, **6**, 35.
Jones, F. A. (1947). *British Medical Journal*, **2**, 441.
Kracke, R. R. (1931). *Amer. J. clin. Path.*, **1**, 385.
—— and Parker, F. B. (1934). *J. Lab. clin. Med.*, **19**, 799.
Madison, F. W., and Squier, T. L. (1934). *J. Amer. med. Ass.*, **102**, 755.
Plum, P. (1934). *Ugeskr. Læg.*, **96**, 916.
—— (1937). *The Clinical and Experimental Investigations in Agranulocytosis, with Special Reference to the Aetiology*, p. 407. Lewis, London.
Rawls, W. B. (1936). *Amer. J. med. Sci.*, **192**, 175.
Rohr, K. (1939). *Helv. med. Acta*, **6**, 611.
Stenbeck, P. (1935). *Nord. med. T.*, **9**, 81.

AGRANULOCYTOSIS SUCCESSFULLY TREATED WITH A.C.T.H.

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The association of pharyngitis with leucopenia was first described in 1902 by Brown and Ophuls, and the name agranulocytosis was later given to the syndrome of severe sore throat, prostration, and extreme reduction or disappearance of granulocytes from the blood which might be followed by sepsis and death (Schultz, 1922). In 1931 Kracke noted that the disease might be caused by certain drugs, and soon afterwards amidopyrine (aminopyrine) was incriminated and the high mortality of the cases caused by this drug was noted (Madison and Squier, 1934). Of all the drugs capable of causing the condition amidopyrine remains still one of the chief offenders: Plum (1937) found it responsible for the large majority of cases in Denmark occurring at this time, reporting 267 cases in which agranulocytosis had followed administration of this drug. Kracke (1938) stated that approximately 80% of drug-induced agranulocytosis was caused by amidopyrine or one of its derivatives. Although many new drugs since then have been incriminated, amidopyrine still remains one of the commoner causes of acute drug-induced agranulocytosis.

Because of this danger of agranulocytosis, amidopyrine has fallen out of favour in this country, though it remains popular on the Continent because of its excellent analgesic properties. What we see now prescribed in its stead are a number of proprietary

compound tablets containing the drug, and new ones are still appearing. Most physicians are not organic chemists and do not always appreciate the dangers of even small amounts of the drug in a compound tablet. There is one further point worthy of note : by substitution of the sodium salt of methyl-sulphonic acid for one of the methyl groups attached to the amino-nitrogen —a chemical manœuvre called sulphonation which results in increased solubility—the drug in this country escapes appearing on any schedule of dangerous drugs and may be purchased across the counter without prescription.

Sodium phenyldimethylpyrazolon methylaminomethane sulphonate ("novalgin" in this country, dipyrone or "novaldin" in the United States), freed from restrictions, remains essentially the same chemical substance as amidopyrine and should in theory be equally dangerous. That it is so is suggested by the fact that of the cases reported by Blake *et al.* (1935), Donnison (1936), Das Gupta (1936), Klumpp (1937), Moloney and Vidoli (1943), and Kneedler (1946) only the last, a mild case in a haemophiliac, lived. While the drug has been considered by all the above authors to be the cause of the condition, it may be argued that the evidence in each case is indirect only and that other factors might have played an important part. Benjamin and Biederman (1936), however, in a human volunteer known to be sensitive to amidopyrine, reproduced symptoms within eight hours of taking 10 gr. (0.65 g.) of novaldin, with a drop in white cells to 2,800 per c.mm. (P. 46%) after 24 hours, complete recovery taking place in 72 hours. The case report which follows pursued the same pattern.

Case History

A housewife aged 65 was admitted to hospital on November 23, 1951. She had had frequent frontal headaches for three to four years, and, as aspirin caused abdominal pain, she took acetanilide on such occasions over a period of two to three years. She remained in good general health and lost no weight. In the past three months she had taken novalgin tablets; the total amount is uncertain, but at least three bottles of 100 tablets were dispensed. Three weeks before admission a severe sore throat began which steadily became worse. She experienced difficulty in swallowing, cough, loss of voice, and increasing weakness. She became febrile. For the 36 hours before admission she was given a total of 4 g. of sulphadimidine. Her previous history was negative but for the fact that since childhood she had been regarded as anaemic.

On admission the patient was seen to be a pale, very ill old lady, drowsy, uncooperative, and occasionally delirious. There was extensive superficial ulceration of the pharynx and soft palate, with much oedema and stringy mucus. The tonsillar glands were enlarged. A few basal rales were heard. The pulse was regular, 100 a minute; the blood pressure 130/80; temperature 101° F. (38.3° C.). A blood count read: Hb, 58%; red cells, 2,300,000 per c.mm.; white cells, 1,400 per c.mm. (lymphocytes 87%, prolymphocytes 4%, monocytes 6%, Türk cells 3%. No polymorphs were present). A throat swab gave a heavy growth of haemolytic streptococci.

Treatment and Progress

Soluble penicillin, 300,000 units intramuscularly four-hourly, with penicillin lozenges, 50,000 units three-hourly, was started. On November 26 2 pints (1.14 litres) of fresh Rh-negative Group O blood was given, and on November 28 10 oz. (284 g.) of packed red cells. Later on the 28th the blood count read : Hb, 98% (14.5 g.); red cells, 4,880,000 per c.mm.; white cells, 2,700 (lymphocytes 94%, monocytes 4%, degenerate polymorphs 2%). She was also given over this period ascorbic acid, 200 mg. thrice daily, pyridoxin, 200 mg. daily, and "betalin" (vitamin B) compound, 2 ml., all by the parenteral route, with ferrous sulphate tablets, 6 gr. (0.4 g.) thrice daily, by mouth. On December 2 folic acid, 10 mg. twice daily, was started.

The patient was isolated from the beginning, and mouth-washes and gargles were given; but she took fluids poorly and became steadily more dehydrated, uncooperative, and ill. Her temperature remained elevated between 99 and 101° F. (37.2 and 38.3° C.), and she became progressively weaker. On December 2 haemolytic streptococci had disappeared from the throat, to be replaced on the 5th by a penicillin-resistant streptomycin-sensitive strain of *Staph. aureus* with subsequent rise in temperature. Streptomycin was started, 1 g. intramuscularly twice daily, on December 6. A chest skiagram was normal. Blood cultures were sterile. For marrow biopsy reports see Table. On December 6 it was obvious there was no response to treatment, and at this stage, 13 days after admission to hospital and five weeks after the commencement of her sore throat, in view of the failure of marrow biopsies or blood counts to improve and

Report on Bone Marrow. Total Nuclear Count

	26/11/51	5/12/51 Day before A.C.T.H. Started	11/12/51	7/1/52
Segmented polymorphs	Nil	Nil	5	11
Non-segmented "	"	"	16	12
Metamyelocytes	"	"	24	18
Myelocytes	1	3	21	16
Premyelocytes ..	3	2	8	3
Blast cells	7	8	2	2
Eosinophils				2
Eosinophilic myelocytes				1
Lymphocytes ..	36	63	12	8
Prolymphocytes ..	7	5		
Monocytes	1		3	1
Plasma cells	10			1
Normoblasts:				
Late	5	2		4
Intermediate ..	19	12	7	18
Early	7	4	1	1
Proerythroblasts ..	2	1	1	2
Reticulum cells ..	2			
Remarks ..	Complete depression of myeloid series	Depression of myeloid series; marrow appears more hypoplastic	Marked granulopoiesis	Normal film

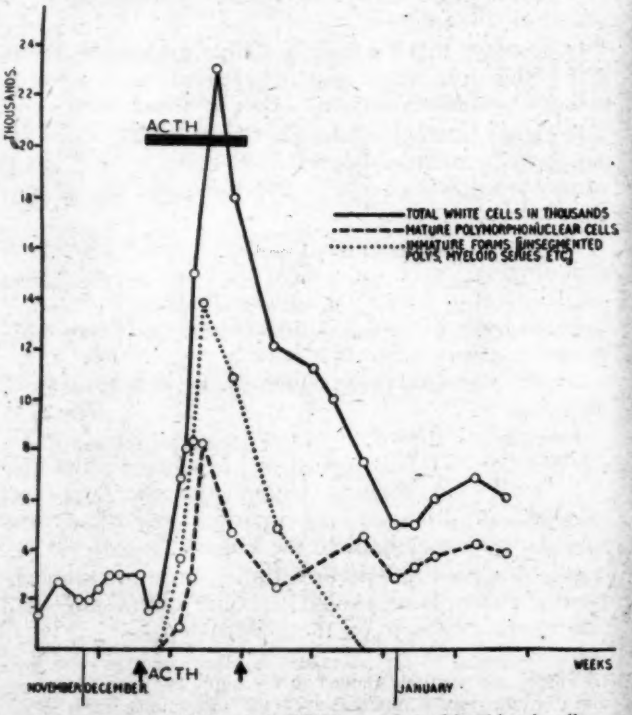

Chart showing effect of A.C.T.H. on the white blood cells.

the steady deterioration in the patient's general condition, it seemed very unlikely that a natural remission would occur, so A.C.T.H. was started, 20 mg. six-hourly for six days, 20 mg. twice daily for two days, and 10 mg. twice daily for two days : a total of 620 mg. over the 10-day period from December 6 to 16.

Progress on A.C.T.H.

After 48 hours her general and local oral condition began to improve and her temperature became normal. The Chart shows the rapid rise in polymorph white cells to a peak of 23,600 on December 12, and marrow biopsy reports (see Table) were equally striking. The white-cell count then fell to normal and remained so. The mouth was completely healed by the twenty-first day of treatment. By the ninth day she was vastly improved mentally and was co-operative. All-round improvement therefore was seen to occur on the third day of treatment, when 200 mg. of A.C.T.H. had been administered, and from that time she never looked back.

Response to Novalgin

After a month, as the patient was perfectly well with an entirely normal blood count, it was decided to try the effect of two tablets—10 gr. (0.65 g.)—of novalgin. These were given at 9 a.m. on January 23, 1952. Four hours later she began to feel unwell. She developed a backache which gradually spread to all limbs and the rest of the body. Immediately after lunch she vomited and was nauseated for the rest of the day. She complained of a headache, frontal in position. Blood counts at this time showed no change, the white cells being 5,800 per c.mm. (neutrophils 3,190 or 55%). The next morning the temperature had risen to 102° F. (38.9° C.), her symptoms were more marked, and shivering attacks occurred. She was definitely ill and had no inclination for food. She looked sallow and puffy around the eyes. Her white-cell count at 10 a.m.—that is, 25 hours after taking the drug—had dropped to 3,600 (neutrophils 75%). The white-cell count, repeated that afternoon and evening, remained low, as it did all next day, polymorphs dropping to 1,680 (42% of 4,000 white cells). A marrow biopsy showed no significant change at this time. Six days after administration of the drug, although the white cells had risen to 8,000, the neutrophils varied from 29 to 44% of the total (1,800 to 3,520). Two compound 5-gr. (0.32-g.) acetanilide tablets (acetanilide 60%, caffeine citrate 9.5%, and sod. bicarb. 30.5%), a drug which she had previously taken, were subsequently given. No symptoms followed their administration, and there were no changes in her blood count.

It was considered unsafe to repeat the experiment with novalgin, for, although the blood count could not be said to be entirely conclusive, the rapid return of her previous symptoms with neutrophil depression was regarded as enough proof that novalgin was the drug responsible for her condition.

Discussion

There is no doubt that in this case A.C.T.H. prevented a fatality ; the patient was, in spite of all treatment, a dying woman when the injections were started. There have been two other cases reported to date, with similar results.

1. The first case was of agranulocytosis caused by a compound sulphadiazine-sulphamezathine(sulphadimidine)-sulphamerazine preparation (Caldwell *et al.*, 1950). Here, although fever was abating before administration of the drug, cortisone given intramuscularly appeared to cure the condition rapidly and effectively, the white cells rising from 975 per c.mm. (no neutrophils present) to 25,400 per c.mm. (88% neutrophils) on the sixth day of treatment. After withdrawing cortisone the white-cell count gradually fell to normal levels over a period of a fortnight. Occasional eosinophils appeared on the ninth day after treatment was stopped.

2. In the second case a male patient, giving hypersensitivity reactions to several substances, developed agranulocytosis after a course of sulphadiazine with chloramphenicol (McMillin, 1951). The former drug was taken to be responsible. A.C.T.H. was started, when, in spite of routine therapy, the patient was *in extremis*, the total white-cell count was only 450 per c.mm. (neutrophils absent), and the marrow biopsy showed almost complete arrest of maturation of myeloid cells at the progranulocyte state. Response was almost identical with that seen in our own case. After 48 hours on A.C.T.H. a marrow biopsy showed early response, even mature polymorphs being seen. Nuclear differentiation had far outstripped cytoplasmic and granular differentiation ; often metamyelocytes with immature blue cytoplasm and azurophil granules were seen. Ten days after treatment was stopped the marrow biopsy showed no sign of maturation defect.

Finch *et al.* (1951), in an investigation into the haematological findings in cases of rheumatoid arthritis treated with cortisone and A.C.T.H., found a significant polymorphonuclear leucocytosis in all patients during treatment, lymphopenia being inconstant and unsustained. The beneficial effect in the two cases noted above and in our own was, however, much more dramatic and rapid than could be explained in this way, and is more likely to have been in the nature of a direct desensitizing action on the marrow itself, and possibly on the circulating neutrophil cells also. Witts (1936) states : "In some cases of idiosyncrasy, such as agranulocytosis from amidopyrine, a mechanism akin to anaphylaxis is present, an initial dose being necessary to sensitize the patient" ; and, again, "it is not known how long amidopyrine sensitivity lasts, but certainly for years and possibly for life." Benjamin and Biederman (1936) think the condition is a hypersensitivity to the drug, "the haemopoietic system acting as the shock organ." There is therefore a rationale for the use of A.C.T.H. or cortisone, and though they may act only in some cases of acute drug-induced agranulocytosis there seems enough evidence to warrant their trial in conjunction with antibiotics, isolation from infection, and other general measures.

Summary

A case of agranulocytosis is reported ; the evidence incriminates novalgin (sodium phenyldimethylpyrazolon methylaminomethane sulphonate ; sodium amidopyrine sulphonate) as the causative drug.

Amidopyrine is well known to be capable of causing agranulocytosis ; novalgin, though escaping Schedule 4, is shown to be also dangerous.

A.C.T.H. produced rapid improvement in the clinical and haematological picture. This improvement began on the third day of treatment and was complete in three weeks. This is the third reported case of drug-induced acute agranulocytosis responding to A.C.T.H. or cortisone.

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References

Benjamin, J. E., and Biederman, J. B. (1936). *J. Amer. med. Ass.*, **107**, 493.
Blake, F. C., Winternitz, M. C., Geiger, A. J., Leonard, J. C., and Opper, L. (1935). *Yale J. Biol. Med.*, **7**, 465.
Brown, P. K., and Ophuls, W. (1902). *Amer. Med.*, **3**, 649.
Caldwell, A. L., Adams, J. W., Anderson, J. F. C., and Dick, A. A. (1950). *J. Canad. med. Ass.*, **62**, 506.
Das Gupta, B. M. (1936). *Indian med. Gaz.*, **71**, 589.
Donnison, C. P. (1936). *British Medical Journal*, **1**, 83.
Finch, S. C., Crockett, C. L., jun., Ross, J. F., and Bayles, T. B. (1951). *Blood*, **6**, 1034.
Klumpp, T. G. (1937). *J. Amer. med. Ass.*, **108**, 637.
Kneedler, W. H. (1946). *British Medical Journal*, **1**, 876.
Kracke, R. R. (1931). *Amer. J. clin. Path.*, **1**, 385.
—— (1938). *J. Amer. med. Ass.*, **111**, 1255.
McMillin, J. S. (1951). *Amer. J. med. Sci.*, **222**, 392.
Madison, F. W., and Squier, T. L. (1934). *J. Amer. med. Ass.*, **102**, 755.
Moloney, W., and Vidoli, M. (1943). *Amer. J. clin. Path.*, **13**, 317.
Plum, P. (1937). *Clinical and Experimental Investigations in Agranulocytosis*. Lewis, London.
Schultz, W. (1922). *Disch. med. Wschr.*, **48**, 1495.
Witts, L. J. (1936). *British Medical Journal*, **2**, 211.

SEVERE AND FATAL PHENOBARBITONE ERUPTIONS

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With the world-wide increasing consumption of phenobarbitone it is comforting, though perhaps surprising, that reports of dangerous reaction to this drug have been so few. Nevertheless it has been estimated that between 1 and 3% of patients taking phenobarbitone develop skin reactions. Recently it has been brought home to us that such skin reactions, far from being innocent, may unexpectedly lead to a dangerous illness and death. We are therefore prompted to report our experience, since we do not believe we have been alone in underestimating the consequences of a phenobarbitone eruption.

In the past 18 months we have seen, at one hospital, four severe cases of phenobarbitone eruption; two of these ended fatally, and a third, equally severe, was saved only by the use of A.C.T.H. Though few similar cases have been reported, this experience suggests that the condition is not a rarity, and it may well be that on a number of occasions the association of this severe illness with phenobarbitone has escaped notice. Since the first report by Chavany and Vannier (1929) of a fatality from skin eruption due to phenobarbitone, 14 fatal cases have been published by Brunsting (1932), Millard (1933), Poole and Wehger (1934), Heckmann (1935), Scarlett and MacNab (1935), Sweitzer and Laymon (1937), Wile and Benson (1940), Winer and Baer (1941), and Sexton *et al.* (1941), and one severe but non-fatal case by Winton (1946). In general the clinical description of these cases has conformed closely to our own.

Case 1

A housewife aged 73 was first seen by one of us (I. B. S.) on April 20, 1950. Six weeks previously she had complained of retrosternal pain and dyspnoea, which had been diagnosed by her doctor as due to a coronary occlusion. He had been unable to find any objective physical signs to support the diagnosis, but as a precaution had kept her in bed and prescribed phenobarbitone, ½ gr. (32 mg.) thrice daily. On April 16 she developed a generalized erythematous maculo-papular eruption. The phenobarbitone was stopped and mepyramine hydrogen maleate ("anthisan"), 100 mg. thrice daily, was given. The skin eruption continued to spread, and her doctor sought further advice. When examined on April 20 she did not appear seriously ill or distressed, but the face, limbs, and trunk were covered with a profuse bluish-red morbilliform eruption which in places was becoming confluent. Her mucous membranes were unaffected, and there was no enlargement of lymph nodes, liver, or spleen. Heart sounds were normal and B.P. was 140/90. It was considered that the eruption was due to an allergic response to the phenobarbitone, and a good prognosis was given in the belief that the drug would soon be eliminated. On April 27, her condition having deteriorated, she was admitted to hospital.

On admission it was apparent that she was gravely ill. She was drowsy, febrile, incontinent, and collapsed. Her B.P. was 90/70, temperature 104° F. (40° C.), and her lips and tongue were dry and cracked. The skin eruption was confluent over the whole body and had become purpuric, and in some areas it was desquamating. Her appearance was that of severe toxaemia with peripheral circulatory failure.

The white blood cells numbered 24,000 (metamyelocytes 4%, polymorphs 75%, lymphocytes 10%, monocytes 8%, eosinophils 3%). Blood non-protein nitrogen was 160 mg./100 ml.; plasma chlorides, 620 mg./100 ml. The cerebrospinal fluid showed no abnormality, and pressure was not raised. The urine contained a cloud of albumin; microscopical examination was negative. An electrocardiogram showed no evidence of infarction. Despite active measures to combat the uraemia, she lapsed into coma and died on May 2.

Necropsy showed passive congestion and oedema of the brain and lower lobes of the lungs. The left ventricle of the heart was hypertrophied and the myocardium infiltrated with fat. Diffuse atheromatous changes were present in the aorta and cerebral and coronary arteries; there was no evidence of coronary thrombosis. The liver was enlarged and showed fatty infiltration. The kidneys were smaller than normal, contracted, and firm, with rough granular surface and narrow cortex. The suprarenals were normal. Microscopical examination of the organs did not add anything of significance to the above findings.

Case 2

An assistant cashier aged 53 was first seen by one of us (A. W. D. L.) on March 29, 1951. His previous history was uneventful; he had had no illnesses of note and had never experienced chest pain on exertion. Some four weeks previously he had been seized with a constricting pain across the upper chest which lasted for approximately two hours; this did not radiate to either arm and was not repeated. It was accompanied by some dyspnoea but no palpitations. His doctor thought it highly probable that he had had a cardiac infarct, and kept him in bed and treated him accordingly. The cardiac condition gave no cause for disquiet, but the patient's increasing anxiety and agitation demanded the prescription of phenobarbitone in a dosage of ½ gr. (32 mg.) four times daily.

Two weeks later a rash developed, and temporarily the barbiturate dosage was reduced. On return, however, to full dosage the rash increased and became generalized. Examination at this time showed him to be depressed and tremulous. The skin was covered with a typical drug rash of maculo-papular type; there was no exfoliation. His general condition was fairly good; the heart appeared slightly enlarged, but sounds were of good quality, with regular rhythm, rate 90; there were no murmurs; B.P. 120/74. There was no indication of cardiac insufficiency. The lungs were clear, the abdomen was normal, and there was no oedema. Examination of C.N.S. was normal apart from a possible extensor plantar response on the right side. Opinion at this time agreed with the diagnosis of a previous small cardiac infarct and a drug eruption due to phenobarbitone. No alarm was felt. It was advised that barbiturates be stopped altogether and promethazine hydrochloride ("phenergan"), 25 mg., be given thrice daily.

During the following week, despite these measures, his condition greatly deteriorated and he was admitted to hospital on April 4. He was extremely ill, being disorientated and incontinent; his temperature ranged between 102 and 104° F. (38.9 and 40° C.). The skin was covered with an exfoliating rash; the mouth and tongue were dry and foul. Venous pressure in the neck was not increased; the heart size was unaltered; there was regular tachycardia (120 to the minute); heart sounds were clear and without murmurs; and the blood pressure was 120/90. There was a small area of consolidation in the axillary segment of the right lung. The abdomen was normal. There were no objective neurological signs other than doubtful bilateral extensor plantar responses.

Examination of the blood showed: haemoglobin, 104%; red cells, 5,100,00; colour index, 1; white cells, 14,000 (band cells 5%, polymorphs 65%, eosinophils 2%, lympho-

cytes 12%, monocytes 16%); sedimentation rate, 24 mm. in one hour. Serum potassium, 20.4 mg./100 ml.; serum sodium, 344 mg./100 ml.; blood urea, 68 mg./100 ml.; serum chlorides, 585 mg./100 ml. An electrocardiogram showed sinus tachycardia, generalized low-voltage curves, a flat or biphasic T wave in lead I and an inverted T wave in the fifth and sixth chest leads. There were no significant Q waves. These changes were compatible with coronary ischaemia, but were by no means typical of a previous cardiac infarction.

The dose of phenergan was increased to 100 mg. twice daily without any improvement in the patient's condition, and on the day after his admission he was given 300 mg. of cortisone intramuscularly, followed by daily injections of 100 mg. There was no improvement in his condition: he became delirious and finally comatose, and died on April 7.

Post-mortem examination of the internal organs revealed few striking changes, but the brain was moderately enlarged and very oedematous, and all blood vessels of the meninges and brain were engorged. The lungs showed confluent patches of recent bronchopneumonia; the trachea and bronchi contained much mucous exudate, and the mucosae were congested and oedematous. The heart was of normal size, the myocardium was flabby, and the aortic valves were calcified. The coronary arteries were not atheromatous, and there was no evidence of coronary thrombosis. Both liver and spleen were enlarged. Microscopical examination of sections from the skin and muscle and numerous organs showed no specific changes.

Case 3

A housewife aged 66 consulted her doctor in July, 1951, because of an attack of giddiness and a feeling of tiredness. No abnormal physical signs were discovered and she was given phenobarbitone, ½ gr. (32 mg.) thrice daily, with improvement in her symptoms. At the end of August she noticed a burning of the skin all over her body, and a bright-red rash appeared. Her doctor stopped the phenobarbitone and gave her anthisan, 100 mg. thrice daily. She then went away to the seaside for two weeks' holiday. While she was there her face became more swollen after exposure to sunlight and she began to feel weak and nauseated, and also complained of dry cough and a pain in the chest on coughing. On her return home on September 15 she was admitted to hospital.

On admission she had a temperature of 104° F. (40° C.) and a pulse of 110, and the skin was covered with a morbilliform erythematous rash, which on the abdomen showed "iris" type lesions. In places the erythema was confluent. Her face and the V of her neck showed considerable oedema of the skin and in places exudation and crusting. Ulceration of the oral mucosa and lips was present. There were no other abnormal physical findings; her B.P. was 148/76.

The blood urea was 52 mg./100 ml. The white cells numbered 12,000 (metamyelocytes 5%, polymorphs 61%, lymphocytes 14%, monocytes 6%, eosinophils 14%). No Hargrave cells were found. An electrocardiogram was normal. A radiograph of chest showed no abnormality. The urine contained no abnormalities. No specific treatment was given. During the next few days the erythema on her trunk and limbs faded and the skin desquamated in a similar fashion to scarlet fever. The skin of her face and V of neck, however, became more crusted and secondarily infected before improvement was shown a week after admission. She continued to have a swinging temperature for 14 days, but this then settled. Her blood urea on September 27 had fallen to 32 mg./100 ml. She was discharged home well three weeks after admission. Two weeks later she developed diffuse alopecia of the scalp hair.

Case 4

A 25-year-old housewife of Italian birth came under our care on September 18, 1951. Some five months previously she had been under investigation in the neurological ward for minor epileptic fits for two years' duration. These were considered to be due to idiopathic epilepsy, and since then she had been taking phenytoin sodium ("epanutin"), 1½ gr. (0.1 g.), thrice daily and phenobarbitone, ½ gr. (32 mg.), twice daily. On September 1 a rash had started on her face and arms, and had gradually spread over the entire body. (She had been admitted on September 14 to an isolation hospital, where, in the belief that her rash was due to an infection, she was given chloramphenicol, 250 mg. six-hourly.) She had become progressively more drowsy and ill, and lapsed into semi-consciousness shortly before admission to our hospital.

On examination she was stuporous, lying in a general attitude of flexion and resenting any attempt to examine her. She had Cheyne–Stokes respiration. The pulse of 100 was soft and thready and the temperature 104° F. (40° C.). Her whole body was covered with a bright-red erythema, and the skin of her face and neck was swollen and desquamating. No abnormal physical signs were found in her chest, abdomen, or central nervous system. The systolic blood pressure was 70; the diastolic pressure was unobtainable. A lumbar puncture revealed clear fluid under normal pressure, with normal cytology. The blood urea was 56 mg./100 ml. The white blood cells numbered 13,000, with a simple polymorphonuclear leucocytosis. The haematologist reported scattered abnormal lymphocytes of a type seen in drug eruptions.

In view of the history of phenobarbitone and epanutin and her resemblance to the other cases, the diagnosis was clearly that of a toxic drug eruption of a most severe type, and she appeared to be moribund. With difficulty, since her veins were tightly contracted, 50 mg. of A.C.T.H. in 1 litre of 5% dextrose was given intravenously during the night. The next morning her temperature had fallen to normal, the Cheyne–Stokes respiration had ceased, she had regained consciousness, and the erythema of her skin was much paler. On September 19, 30 mg. of A.C.T.H. was given in dextrose, and on the 20th and 21st 20 mg. On September 21 her temperature, which had remained normal, rose again to 104° F. (40° C.). At first this was thought to be due to thrombophlebitis in the vein used for the infusion, but on the next day signs of pneumonia were present at the right base. The A.C.T.H. was therefore stopped. Despite the pneumonia her general condition had improved and her skin was now pale but peeling. A chest radiograph showed consolidation of the right lower lobe and the left upper lobe.

Despite the presence of a penicillin-resistant staphylococcus in her sputum, the pneumonia responded slowly to chloramphenicol, 500 mg. six-hourly, and she was discharged home well on October 25. It was considered too hazardous to let her take epanutin and phenobarbitone again for the control of her epilepsy, and with the consent of the neurologist she was advised to take only bromides. When seen two weeks later she had diffuse alopecia.

Discussion

Drug eruptions due to acquired hypersensitivity have increased in number with the greater use in recent years of complex organic compounds. For example, phenylethylhydantoin ("nirvanol") attained notoriety on account of the almost inevitable drug rash which followed its use. Barbiturates form an important group of chemicals. According to Potter and Whitacre (1944), the long-acting barbiturates, such as phenobarbitone, cause skin reactions more often than the short-acting barbiturates, such as pentobarbital sodium ("nembutal") and sodium propylmethylcarbinylallyl barbiturate (quinalbarbitone, "seconal"). Commonly, the eruptions are harmless and will subside on withdrawal of the offending drug. It is therefore disturbing to find that in some cases of acquired hypersensitivity to phenobarbitone the eruption continues to extend, and that constitutional symptoms may appear some weeks after the drug has been stopped.

The amount of phenobarbitone which has been given before the eruption and illness appear may vary greatly, and in Chavany and Vannier's (1929) first case 1½ gr. (0.1 g.) daily for nine days proved fatal. In our cases the highest daily dosage was 2 gr. (0.13 g.). Our diagnosis was based on the characteristics of the skin eruptions, the history of exposure to phenobarbitone, and the clinical course, which conformed closely to other accounts of phenobarbitone eruptions. In view of the risk involved no attempt was made to establish the diagnosis by deliberate re-exposure to the drug. Tests of this type, according to Sulzberger and Baer (1945), may in any case be misleading, since a patient in a refractory phase will fail to react to the drug which caused the eruption. They also state that skin tests are of no value in drug eruptions of this kind.

In our fourth case the possibility that epanutin may have caused the eruption cannot be excluded, but the clinical condition and course of the illness was so similar to the other three cases that we are more inclined to incriminate phenobarbitone. The cause of death in these cases is far from obvious.

In the necropsy reports of other fatal cases no specific changes were found, and death was usually ascribed to terminal bronchopneumonia. In the cases described by Millard (1933) and Poole and Wehger (1934) chronic nephritis was also reported, but renal damage has not been a general finding. In our first case there was certainly chronic renal disease, but this was not found in our other fatal case. It is probable that where there is defective excretion phenobarbitone hypersensitivity is more likely to be fatal. Cerebral irritation was a feature of three of our cases, but there was no rise in cerebrospinal-fluid pressure as was found by Jenkins (1949) in a remarkable case of phenobarbitone idiosyncrasy in which the patient twice became unconscious a few hours after a small dose of the drug. Cerebral oedema, however, was found at necropsy in both of our fatal cases. No evidence of disseminated lupus erythematosus or periarteritis nodosa was found in any of the cases, though it is interesting that Rennie *et al.* (1951) describe periarteritis nodosa as a sequela of an exfoliative dermatitis due to phenobarbitone. It can surely only be coincidence that in two of our cases a clinical but unsubstantiated diagnosis of coronary thrombosis had earlier been made, though Winton (1946) has described severe phenobarbitone eruption in a proved case of myocardial infarction.

On the basis of this small experience it would not be fruitful to speculate too far on the nature of this illness. Nevertheless, the absence of specific pathological changes, the fulminant course, and the appearance of these patients in the terminal stages suggest that they died from a biochemical cause. It may be that this conception, nebulous though it be, receives some support from the recovery of our fourth patient, after treatment with A.C.T.H. when in an apparently moribund condition. The response in this case was so remarkable that we have no doubt that this drug must be given further trial in similar cases.

It is not necessarily surprising that cortisone, on the other hand, proved ineffective, for experience with these two drugs in the treatment of disseminated lupus erythematosus and other collagen diseases (Irons *et al.*, 1951) has shown that A.C.T.H. has much the more rapid action; also it must not be forgotten that when given by the intravenous route, as in our case, the potency of A.C.T.H. is greatly enhanced.

Summary

Four cases of severe allergic reactions to phenobarbitone given in therapeutic dosage are described.

It is suggested that the potential dangers of phenobarbitone skin eruptions may not be sufficiently appreciated.

Post-mortem examination in these cases, as in those previously published, has shown no specific pathological changes.

The life-saving effect of intravenous A.C.T.H. in one case and the failure of cortisone to influence another is reported.

REFERENCES

Brunsting, L. A. (1932). *Proc. Mayo Clin.*, **7**, 618.
Chavany, J. A., and Vannier, P. E. (1929). *Progr. méd., Paris*, **44**, 1685.
Heckmann, M. (1935). *Z. Kinderheilk.*, **57**, 358. Quoted by Wile and Benson (1940).
Irons, E. N., Ayer, J. P., Brown, R. G., and Armstrong, S. H., jun. (1951). *J. Amer. med. Ass.*, **145**, 861.
Jenkins, C. M. (1949). *Ann. Allergy*, **7**, 346.
Millard, R. J. (1933). *Med. J. Aust.*, **2**, 518.
Poole, A. K., and Wehger, R. T. (1934). *J. Amer. med. Ass.*, **102**, 745.
Potter, J. K., and Whitacre, R. J. (1944). *Ann. intern. Med.*, **21**, 1041.
Rennie, J. B., Milne, J. A., and Sommerville, J. (1951). *British Medical Journal*, **1**, 383.
Scarlett, E. P., and MacNab, D. S. (1935). *Canad. med. Ass. J.*, **33**, 635.
Sexton, D. L., Pike, G. M., and Nielson, A. (1941). *J. Amer. med. Ass.*, **116**, 700.
Sulzberger, M. B., and Baer, R. L. (1945). *Year Book of Dermatology and Syphilology*. Year Book Publishers, Chicago.
Sweitzer, S. E., and Laymon, C. W. (1937). *Minn. Med.*, **20**, 92.
Wile, U. J., and Benson, J. A. (1940). *Ann. intern. Med.*, **13**, 1243.
Winer, N. J., and Baer, R. L. (1941). *Arch. Derm. Syph., Chicago*, **43**, 473.
Winton, S. S. (1946). *J. Amer. med. Ass.*, **130**, 1012.

CHOLESTEROL TOLERANCE IN CORONARY THROMBOSIS

BY

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This investigation was planned to determine whether the dietary cholesterol content bore any relation to coronary thrombosis, and, in particular, to learn if patients suffering from coronary thrombosis showed intolerance to cholesterol.

The subject of cholesterol and atheroma has received much attention of late, especially in America, and recently has been reviewed by Firstbrook (1951), who pointed out the importance of coronary artery disease as a cause of death and disability, defined the terminology and pathology, and gave seven main lines of evidence suggestive of plasma cholesterol being implicated in the development of atherosclerosis.

It may be stressed here that cholesterol feeding has proved to be the most consistent method of producing atheroma in experimental animals. Dauber and Katz (1942, 1943), using chicks, showed that atheromatous lesions could be produced consistently, even in omnivora, through a high cholesterol diet alone. Dauber (1944) proved that chicks were suitable experimental animals, when used before six months. The failure of high cholesterol feeding to produce atheroma, or even to raise the blood cholesterol, in some omnivora (Duff, 1935), in contrast to the constant success among herbivora, is possibly explained by the difference in cholesterol storage shown by Menschick and Page (1933), who found that in rabbits the distribution of cholesterol was diffuse, while in cats the distribution was confined mainly to the liver. This difference may account for the difficulty in producing hypercholesterolaemia in omnivora. Nevertheless, no other method in the experimental field is as successful as cholesterol feeding in producing lesions morphologically identical to human atherosclerosis.

Among humans, atherosclerosis often occurs in diseases associated with hypercholesterolaemia—for example, in diabetes (Bowen *et al.*, 1939), myxoedema (Bruger and Rosenkrantz, 1942), nephritis (Weinhouse, 1943), and hereditary xanthomatosis (Boas and Aldersberg, 1945). It would therefore appear that even in humans the presence of hypercholesterolaemia predisposes to the production of atherosclerosis, although,

in view of the common sites for atheroma, the additional factor of local stress and strain on the vessel wall must be considered. That coronary artery disease is associated with hypercholesterolaemia has often been confirmed, the most recent careful investigation being by Basu and Stewart (1951).

Present Investigation

Many authorities have advocated a low cholesterol diet in the management of coronary thrombosis (Dock, 1947; Burns, 1948; Plotz, 1949). The present investigation was carried out to show the immediate post-absorptive changes after a test dose of cholesterol, and the effect of a prolonged low cholesterol diet on the incidence of coronary thrombosis.

Immediate Post-absorptive Changes

Two observations led one to expect there might be a significant post-absorptive rise in blood cholesterol concentration. First, Steiner and Domanski (1943) reported fluctuation from month to month in the cholesterol levels of 15 cases of atherosclerosis, in contrast to the constant level reported by Bloor (1943) in normal subjects. Morrison, Hall, and Gonzales (1949) confirmed this instability in cases of coronary artery disease. Secondly, Morrison, Berlin, and Gonzales (1949) found a high rise in all blood lipid constituents after a fatty meal in 25 cases of atherosclerosis. Unfortunately, they did not quote the figures of this rise, nor were the quantities in their diet specified, but the high rise reported was contrary to the findings of Bruger and Somach (1932) and Chaikoff *et al.* (1934), who had shown that ingestion of food had no appreciable effect, early or late, on the blood cholesterol in the normal subject.

In the present investigation into the immediate post-absorptive changes in the blood-cholesterol levels, it was decided to employ a test analogous to the "glucose-tolerance test" used in the diagnosis of diabetes mellitus. Brun (1939) described such a test using 80 g. of olive oil with 4 g. of cholesterol added. This test dose, employed in the investigation of the lipid changes in patients with manic-depressive psychosis, showed increases in the serum cholesterol of 5 to 31 mg. per 100 ml. within two to six hours. Turner and Steiner (1939) gave a breakfast of eggs, buttered toast, and milk, with 20 g. of cholesterol added. They too reported little change in the blood cholesterol over 24 hours. Blotner (1935) described a fat-tolerance test, using as a test dose 500 ml. of 20% cream. His investigation showed that the obese had a greater rise in blood cholesterol than the malnourished. As substances such as cream and eggs are difficult to obtain, and as olive oil is not easy to take, a fresh means of giving cholesterol was devised.

TABLE I.—*Results*

Case No.	Age and Sex	Condition	B.P.	Fat in Diet*	Build	Cholesterol-tolerance Test. Serum Cholesterol in mg. per 100 ml.						
						Fast.	2 hrs.	4 hrs.	6 hrs.	8 hrs.	Maximum Variation	Occurring at
Group 1 patients:												
1	18 M	Pneumonia (convalescent)			Av.	259	258	278	275	292	+33	8 hours
2	29 M	Healthy subject			,,	250	245	256	259	268	+18	8 ,,
3	39 M	,, ,,			Under	214	206	228	243	242	+29	6 ,,
4	41 M	,, ,,			Over	254	282	282	270	269	+28	2 ,,
5	57 M	Anxiety state			,,	246	256	261	266	266	+20	6 ,,
6	62 F	Obesity			,,	374	372	396	402	400	+28	6 ,,
7	36 F	Rheumatoid arthritis			Av.	177	175	183	167	—	+6	4 ,,
8	55 F	,, ,,			Over	324	325	338	330	347	+23	8 ,,
9	56 F	,, ,,			Av.	268	252	261	277	286	+18	8 ,,
10	47 M	Chronic bronchitis			Over	280	326	324	268	304	+46	2 ,,
11	64 M	,, ,,			Under	173	220	212	198	200	+47	2 ,,
12	60 M	Bronchial carcinoma			,,	182	187	166	174	161	−21	8 ,,
13	66 M	Congestive cardiac failure			Av.	184	184	191	212	204	+28	6 ,,
14	72 M	Cholangio-hepatitis (convalescent)			,,	188	176	176	198	222	+34	8 ,,
15	18 F	Thyrotoxicosis			,,	164	164	166	169	182	+18	8 ,,
16	51 F	,,			Under	180	186	186	204	192	+24	6 ,,
17	49 F	,,			,,	196	222	—	192	181	+26	2 ,,
18	51 F	Malignant exophthalmos			Over	328	324	338	293	282	−46	8 ,,
19	47 F	Nephritis, type 1			Av.	204	218	228	214	213	+24	4 ,,
20	53 F	Pyelonephritis			Under	191	189	194	198	189	+7	6 ,,
					Mean values	232	238	245	240	247		
Group 2 patients:												
21	34 M	Nephritis, type 2			Av.	1,204	1,408	1,408	1,436	1,412	+232	6 hours
22	54 F	,, ,,			,,	289	323	318	310	335	+46	8 ,,
23	61 F	,, ,,			,,	512	552	563	587	—	+75	6 ,,
24	56 F	Diabetes mellitus			,,	238	276	249	252	298	+60	8 ,,
25	53 F	Myxoedema			Over	295	348	417	408	408	+122	4 ,,
25	53 F	,, (receiving thyroid)			,,	250	281	248	250	251	+31	2 ,,
26	62 F	,,			,,	405	504	529	529	457	+124	4 ,,
26	62 F	,, (receiving thyroid)			,,	316	329	320	300	313	−16	6 ,,
27	36 F	,, ,, ,,			Av.	261	255	255	252	258	−9	6 ,,
28	59 F	,, ,, ,,			Over	319	321	319	283	303	−36	6 ,,
29	62 F	,, ,, ,,			,,	386	361	386	412	326	−60	8 ,,
30	64 F	,, ,, ,,			,,	424	446	432	438	378	−46	8 ,,
31	67 F	,, ,, ,,			Av.	314	269	286	271	—	−45	2 ,,
32	51 M	Pulm. tuberc.; nephritis, type 2			Under	356	341	359	351	354	−15	2 ,,
Group 3 patients:												
33	41 M	Coronary thrombosis	134/76	Av.	Av.	245	246	246	252	248	+7	6 hours
34	42 M	,, ,,	175/105	,,	,,	246	249	240	247	238	−8	8 ,,
35	45 M	,, ,,	150/90	+	Over	235	233	231	237	273	+38	8 ,,
36	49 M	,, ,,	110/70	Av.	,,	272	265	267	272	—	−7	2 ,,
37	53 M	,, ,,	175/110	,,	,,	330	341	336	329	338	+11	2 ,,
38	56 M	,, ,,	145/75	+	,,	212	214	222	212	210	+10	4 ,,
39	56 M	,, ,,	130/90	Av.	,,	325	342	332	334	334	+17	2 ,,
40	58 M	,, ,,	140/90	,,	,,	200	241	225	194	192	+41	2 ,,
41	59 F	,, ,,	100/75	,,	Av.	381	365	391	380	376	−16	2 ,,
42	60 M	,, ,,	135/90	,,	Over	324	340	328	337	324	+16	2 ,,
43	62 F	,, ,,	164/110	,,	,,	262	269	284	283	286	+24	8 ,,
44	62 M	,, ,,	146/106	,,	Under	171	182	156	179	157	−15	4 ,,
45	65 M	,, ,,	125/80	,,	Over	272	292	288	260	266	+20	2 ,,
46	66 M	,, ,,	185/105	++	Under	264	264	264	267	264	+3	6 ,,
47	67 M	,, ,,	150/80	Av.	Over	274	278	274	256	266	−18	6 ,,
48	59 M	Intermittent claudication	180/90	,,	,,	356	341	359	351	354	−15	2 ,,
49	63 M	,, ,,	160/100	,,	,,	285	296	296	284	295	+11	2 ,,
50	65 F	,, ,,	180/100	,,	Av.	425	433	441	464	449	+39	6 ,,
					Mean values	282	288	288	285	286		

* In terms of standard British rations.

Cholesterol-tolerance Test

The test meal consisted of 5 g. of dry powdered cholesterol mixed into 25 g. of margarine: 5 g. of cholesterol was chosen as representing approximately 25 times the average daily intake in normal diet, and margarine was chosen as the vehicle as it is free from cholesterol and also because its fatty acid content is required for the absorption of cholesterol. It was found that this mixture could not be distinguished in taste from ordinary domestic margarine. The entire cholesterol–margarine mixture was spread on toast and flavoured with marmalade or jam, according to the patient's wishes. Tea, without milk but with or without sugar, was allowed. This comprised the test meal.

Cook (1942) reported that only a small quantity of the cholesterol ingested could be recovered from the faeces. Therefore absorption of most of the cholesterol was assumed. Furthermore, Group 2 in the present investigation (see results) showed that this meal could significantly raise the blood-cholesterol level in some patients.

The procedure of the test was that after the patient had fasted overnight for 12 hours the fasting specimen of blood was withdrawn. Thereafter, breakfast consisting of the test meal was given. Two, four, six, and eight hours later, further specimens of blood were taken. During the period of the test the patient's activities were restricted. Additional small quantities of carbohydrate foods were permitted as hunger demanded. Fluid, free from milk, was allowed as required. At the completion of the test all five specimens of blood were examined for cholesterol content by a modified Bloor method, this method having been found to be accurate to within 5 mg.

Material.—Cholesterol-tolerance tests were carried out on 50 patients, who were divided into three groups:

Group 1.—Healthy subjects and patients free from symptoms and signs of atherosclerosis who were not suffering from conditions associated with hypercholesterolaemia.

Group 2.—Patients suffering from conditions known to be associated with hypercholesterolaemia.

Group 3.—Patients suffering from atherosclerosis. The majority were patients with coronary thrombosis, but a small group with intermittent claudication (arteriosclerosis obliterans) was included. Coronary thrombosis was diagnosed only if there was both clinical and electrocardiographical evidence. In these subjects coincidental conditions associated with hypercholesterolaemia were excluded clinically.

Results (Table I)

Group 1.—Of the 20 subjects in this group, 16 showed a maximum variation by an increase within 5–35 mg. per 100 ml., a finding that is in keeping with the results obtained by Brun (1939); two had an increase over 35 mg. per 100 ml. —the figures being 46 and 47 mg. per 100 ml.; and two had a maximum variation shown by a fall in serum cholesterol, their figures being 21 and 46 mg. per 100 ml. below the fasting value. The mean values for this group showed a maximum increase of 15 mg.

Group 2.—Three patients with uncomplicated type 2 nephritis showed increases varying from 46 to 232 mg. per 100 ml. above the fasting level. The degree of hypercholesterolaemia in these patients could not be related to the plasma protein findings. One patient with diabetes mellitus showed an increase of 60 mg. per 100 ml. Two patients with untreated myxoedema showed increases of 122 and 124 mg. per 100 ml. The cholesterol-tolerance test, when repeated on these patients after beginning thyroid therapy, showed curves similar to those in Group 1. Five other cases of myxoedema receiving thyroid showed maximum variations by falls varying from 9 to 60 mg. per 100 ml. below fasting values. One patient with type 2 nephritis complicated by pulmonary tuberculosis showed a fall of 15 mg. per 100 ml.

Group 3.—Of the 18 patients in this group 15 showed maximum variations within ±35 mg. of fasting levels. Only three showed rises over 35 mg., the values being 38, 39, and 41 mg. per 100 ml. The mean values of the cholesterol-tolerance test in the group showed a maximum increase of 6 mg. The average fasting level was above normal, the normal average in this hospital's laboratory being 207 mg. per 100 ml. ± 34. Only four of the individual fasting levels fell within this range. The degree of variation after cholesterol ingestion could not be correlated to age, sex, blood pressure, build, or duration of symptoms.

Effect of Prolonged Low Cholesterol Diet

In the atherosclerotic group notes were made of the patient's dietetic habits, particularly for the past 10 years, when their dietetic habits were compared against the standard British rations. Butter, cheese, eggs, milk, bacon, butcher's meat, and lard being rationed, and "offal" such as liver and kidney being very scarce, the only remaining rich source of cholesterol was fish. Margarine made from vegetable oils contains no cholesterol.

With allowance for supplementing the rations with fish, it was calculated that the average British diet for the past 10 years contained less than 200 mg. of cholesterol daily.

TABLE II

Food	mg. Cholesterol* per 100 g. Fresh Weight	Approx. Weekly British Ration in g.	Approx. Weekly Cholesterol Intake
Butter	240	120	290
Cheese	42	120	50
Eggs	313	70	200
Fish	56 (approx.)	Off ration: allowing 500	280
Flesh	68 "	250	170
Kidney	310	—	—
Lard	110	120	130
Liver	140	—	—
Milk	12	1,500	180
		Total	1,300

* Average figures from Cook (1942).

The standard ration was taken as average. In the atherosclerotic group, only in two cases was this significantly exceeded (Table I). In the remaining 16 cases the patient's normal diet closely approximated the ration scale in the cholesterol-containing foods. Therefore for the past 10 years the cholesterol intake for these patients has been low. The blood cholesterol levels showed no relationship to the patient's diet.

Discussion

The results of the cholesterol-tolerance test showed no significant difference between Group 1 and the atherosclerotic group. Not only did both mean curves show no significant rise, but also in Group 1 and the atherosclerotic group the majority of the individual curves fell within the limits found in psychotics by Brun (1939). These results would therefore appear to show that in the atherosclerotic patients there is no abnormal post-absorptive increase in blood cholesterol and therefore atherosclerosis is not the cumulative result of temporary increase in blood cholesterol.

Although Schoenheimer and Breusch (1933) and Cook (1942) have shown that cholesterol can be synthesized in the body according to its needs, and that dietary restrictions did not reduce the blood cholesterol, the fact that atherosclerosis decreased in Germany during the fat-shortage years after the 1914–18 war (Aschoff, 1924) influenced many to treat coronary thrombosis by a low fat diet. However, the present restrictions on the diet of the British population has not reduced the number of deaths from coronary thrombosis. In fact, coronary thrombosis is rapidly increasing despite a low cholesterol content in the British rations for over 10 years, a period much longer than reported in the American therapeutic trials.

It would therefore appear from the results of the cholesterol-tolerance test, and also from the failure of prolonged low cholesterol feeding to reduce the incidence of coronary

thrombosis, that mere restriction of dietary cholesterol serves no purpose, immediate or late, in the prevention or treatment of coronary artery disease, and that the development of atheroma is not dependent on the cholesterol in the diet. This conclusion is in agreement with the findings of Keys *et al.* (1950), who showed that lowering of the blood cholesterol cannot be achieved by mere reduction of dietary cholesterol, but only by a diet entirely free from cholesterol, such as in a rice diet. Humans therefore resemble the majority of omnivora, in whom it has been shown that blood cholesterol concentration is not readily influenced by ingested cholesterol (Duff, 1935).

The present investigation finds no justification for the restriction of the cholesterol content in the diet of patients suffering from coronary thrombosis, as advocated by some authorities.

The results in Group 2 are of interest in confirming that the test dose of cholesterol was sufficient to raise the blood cholesterol significantly in patients suffering from some diseases, and therefore in the atheroma group the rise, which did not exceed the limits reported by Brun (1939), was not due to an inadequate dose of cholesterol. But of even greater interest was the effect of thyroid therapy on the cholesterol-tolerance tests of the myxoedematous patients. With one exception, which was in a myxoedematous patient not long on thyroid and later found to require a larger dose, the cholesterol-tolerance test showed, after the ingestion of cholesterol, a fall of the serum cholesterol below fasting levels. Turner (1933) showed that when thyroid was administered along with cholesterol feeds, atheroma failed to appear in rabbits. Herrmann (1946, 1947a, 1947b) also found thyroid effective in lowering the blood cholesterol in coronary thrombosis, but in view of the undesirable effect on the metabolic rate its use in coronary thrombosis cannot be advocated. He also showed that choline was even more effective, and Morrison and Gonzales (1949) reported worthwhile results in the treatment of coronary thrombosis with choline. This would appear to be a more hopeful measure in the correction of the hypercholesterolaemia of coronary thrombosis than dietetic restrictions.

Summary and Conclusions

The method of a cholesterol-tolerance test is described.

The results showed that there was no abnormal post-absorptive increase in blood cholesterol in coronary thrombosis. Reasons are given for considering that atheroma is not dependent on the cholesterol content of the diet, and that treatment of coronary thrombosis by a low cholesterol diet is unlikely to be of benefit.

The association of hypercholesterolaemia with atherosclerosis was once more confirmed.

The results of this cholesterol-tolerance test suggested that there might be intolerance of ingested cholesterol in a small group of patients—namely, those with nephritis (type 2), diabetes mellitus, and myxoedema.

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REFERENCES

Aschoff, L. (1924). *Lectures on Pathology*. Hoeber, New York.
Basu, D. P., and Stewart, C. P. (1951). *Edinb. med. J.*, **58**, 392.
Bloor, W. R. (1943). *Biochemistry of the Fatty Acids*. Reinhold, New York.
Blotner, H. (1935). *Arch. intern. Med.*, **55**, 121.
Boas, E. P., and Aldersberg, D. (1945). *J. Mt Sinai Hosp.*, **12**, 84.
Bowen, B. D., Regan, J. S., and Koenig, E. C. (1939). *Ann. intern. Med.*, **12**, 1996.
Bruger, M., and Rosenkrantz, J. A. (1942). *J. clin. Endocrinol.*, **2**, 176.
—— and Somach, I. (1932). *J. biol. Chem.*, **97**, 23.
Brun, G. (1939). *Changes in the Lipid Content of Serum in Patients with Manic-Depressive Psychosis*. Lewis, London.
Burns, F. J. (1948). *R.I. med. J.*, **31**, 103.
Chaikoff, I. L., McGavack, T. H., and Kaplan, A. (1934). *J. clin. Invest.*, **13**, 1.
Cook, R. P. (1942). *Nutr. Abstr. Rev.*, **12**, 1.
Dauber, D. V. (1944). *Arch. Path.*, **38**, 46.
—— and Katz, L. N. (1942). Ibid., **34**, 937.
—— —— (1943). Ibid., **36**, 473.
Dock, W. (1947). *J. Amer. med. Ass.*, **134**, 1197.
Duff, G. L. (1935). *Arch. Path.*, **20**, 81, 259.
Firstbrook, J. B. (1951). *British Medical Journal*, **2**, 133.
Herrmann, G. R. (1946). *Tex. St. J. Med.*, **42**, 260.
—— (1947a). *Exp. Med. Surg.*, **5**, 149.
—— (1947b). *Trans. Ass. Amer. Phys.*, **60**, 160.
Keys, A., Mickelsen, O., Miller, E. V. O., and Chapman, C. B. (1950). *Science*, **112**, 79.
Menschick, W., and Page, I. H. (1933). *Hoppe-Seyl. Z.*, **218**, 95.
Morrison, L. M., Berlin, P., and Gonzales, W. F. (1949). *Amer. Heart J.*, **38**, 477.
—— and Gonzales, W. F. (1949). Ibid., **38**, 471.
—— Hall, L., and Gonzales, W. F. (1949). Ibid., **38**, 478.
Plotz, M. (1949). *J. Amer. med. Ass.*, **139**, 623.
Schoenheimer, R., and Breusch, F. (1933). *J. biol. Chem.*, **103**, 439.
Steiner, A., and Domanski, B. (1943). *Arch. intern. Med.*, **71**, 397.
Turner, K. B. (1933). *J. exp. Med.*, **58**, 115.
—— and Steiner, A. (1939). *J. clin. Invest.*, **18**, 45.
Weinhouse, S. (1943). *Arch. Path.*, **35**, 438.

SOME OBSERVATIONS ON SUBTERTIAN MALARIA

BY

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As one becomes familiar with the features of subtertian malaria one is struck by the inconstant clinical picture which it presents. I therefore venture to record my impressions gained from several years' experience and several thousand cases of this disease.

Whereas in benign tertian and quartan malaria the clinical picture is more or less uniform, cases of subtertian malaria differ considerably. To confirm my previous impressions I have analysed 50 consecutive cases of acute subtertian malaria admitted to hospital. It is of course impossible to draw any rigid conclusions from such a small number of cases : this article merely attempts a general discussion of the clinical features of subtertian malaria, and the cases analysed do no more than lend support to my contentions. The series analysed consists of 12 adult males, 6 children, and 32 adult females. All these patients were Africans, except one child, who was a European.

Symptoms

Rigors.—One or more rigors are usually regarded as typical of malaria, taken in conjunction with other symptoms and signs. In subtertian malaria, however, they are by no means invariably present, and my impression is that they occur in only about two-thirds of cases. In malarial children convulsions do not as a rule replace rigors as they do in some other systemic infections. Rigors are unlikely to occur in the early or incubation period of subtertian malaria while the temperature is high and continuous (see below). In the present series 60% of patients had rigors, but this figure is probably low. The rigor itself, consisting of the cold stage, the hot stage, and the sweating stage, is in many cases typical, but a large proportion of patients complain only of feeling cold, and never show the hot and the sweating stages. A fair number complain of feeling cold, say, in the afternoon and, without feeling hot, sweat profusely during the night. It is worth while to keep in mind these different patterns of rigors.

Headache.—Severe headache is usual in malaria, and is seldom absent. Almost every febrile patient has some headache, but the malarial headache is characterized not so much by its severity as by its situation. It is in my experience both frontal and occipital, and extends down into the neck. In this series headache was present in 88% of patients.

Vomiting.—This is regarded as typical of the bilious remittent form of malaria, but, in fact, it occurs in most forms of this disease, and severe intractable vomiting should on occasion warn one of impending cerebral malaria.

Vomiting as a symptom is not common in subtertian malaria, and in the present series only 24% complained of this symptom.

Feverishness.—This is common in malaria patients, and subtertian malaria is no exception. Often feverishness and sweating occur together, with or without a rigor. In the present series 90% complained of feverishness.

Generalized Pains.—In this part of the world "pains all over the body" are very common, and may mean anything from a subclinical vitamin deficiency to influenza and malaria. Generalized body pains, together with one or more of the symptoms mentioned above, are, however, common in malaria patients, and are more often present than absent. In the present series 72% complained of this symptom, together with other symptoms. One patient (Case 1) had "pains all over the body" only.

Uncommon Symptoms.—Diarrhoea, with or without blood and/or mucus in the stools, is an occasional symptom, usually accompanied by other features of malaria, though in Case 3 diarrhoea was the only feature present at the beginning. Coma is uncommon, except in cerebral malaria, which is not discussed here. Jaundice, a feature sometimes seen in severe attacks of subtertian malaria, is not common in my experience, and in the present series did not occur.

Signs

Pyrexia.—This is usual, and is to be expected in all cases of malaria. Absence of pyrexia throws considerable doubt on the diagnosis of malaria. In the present series 98% were pyrexial, the only apyrexial case (Case 1) presenting features which merit separate discussion. The highest temperature recorded in this series was 105.4° F. (40.8° C.), the lowest 99° F. (37.2° C.). In all these cases the average pyrexia was 102.6° F. (39.2° C.), a not inconsiderable fever. The average duration of pyrexia in all treated cases was two and a half days, though there were great individual variations. Thus the shortest duration of pyrexia was one day, and the longest nine days (Case 2).

Malarial pyrexia, even that of the subtertian variety, is said to be intermittent. A large proportion of patients, however, show a remittent fever, and only where the typical rigors are present is it intermittent. In a number of cases one even sees a continuous pyrexia for several days. In the present series the fever was intermittent in 42%, remittent in 44%, continuous in 12%, and absent in 2%. The fall of temperature usually occurs by crisis, but in some it falls by lysis. In the present series 88% falls occurred by crisis and the remainder by lysis.

Subtertian malaria is particularly apt to show a continuous high temperature in the prodromal or "incubation" period. In the absence of treatment this will become intermittent after some days, when the rigors, if any, appear. Otherwise there is a fall by lysis or crisis, with or without treatment. If treatment is instituted early a fall by crisis can be expected, and rigors may then never occur. A recurrence of pyrexia is occasionally seen even after treatment has become effective, and may last two or three days. There was such a recurrence in 24% of cases in the present series.

Palpable Spleen.—In subtertian malaria a large percentage of patients never develop a palpable spleen: in this series splenomegaly was found in 56% of cases, which is in accord with my previous experience. The degree of splenomegaly varies considerably. In acute attacks occurring in subjects of chronic malaria the spleen tends to be large; in other cases only the tip may be palpable. On the average the usual degree of enlargement is two fingerbreadths below the costal margin. It is interesting to note that in one patient, not in the present series, who had chronic malaria, the spleen was palpable per vaginam.

Positive Blood Smear.—All patients in the present series had at least two thin smears taken. Thick smears were not done, as my experience of them is not sufficient for their competent interpretation. Of the cases described here, 60% had positive blood smears, but this figure is very low. Under ideal conditions experienced observers, using thick as well as thin smears, should obtain nearly 100% positives. In this series only smears showing the typical ring forms of *Plasmodium falciparum* were labelled positive. Indeed, other forms were not seen at all. A point worth noting is that if smears taken at the height of the pyrexia fail to show the parasites the latter may at times be found in smears taken when the temperature is subnormal.

Herpes Febrilis.—This is mentioned because from some reports it seems to be common. In my experience herpes febrilis in subtertian malaria is uncommon: in the present series it was absent.

Diagnosis

Of the cases analysed here 72% were diagnosed as malaria when first seen, and from my experience I would say that about three-quarters of patients show sufficiently characteristic initial symptoms and signs to make the diagnosis almost certain. The remainder, barring the afebrile case, were sent to hospital as cases of pyrexia of unknown origin, and one patient was sent in as a case of splenitis (Case 6). Of the P.U.O.s none showed evidence of any other disease. In all these cases the occurrence of rigors and/or splenomegaly, or the demonstration of parasites in the blood smear, clinched the diagnosis, though occasionally a patient may need exhaustive investigation before suspicion is either confirmed or negatived.

Treatment

In the acute attack quinine, mepacrine, or proguanil is used. It is interesting to compare the effect of quinine and proguanil in the acute case. Quinine was given as the dihydrochloride, in doses of 30 gr. (2 g.) a day for three days, and 15 gr. (1 g.) a day for four days. Children and infants were given proportionately less. Proguanil was used according to two schedules: (1) four tablets (0.4 g.) the first day, then two tablets (0.2 g.) daily for five days; and (2) one tablet three times a day for six days. There was no noticeable difference in the results obtained by these schedules.

In my experience there is no doubt about the superiority of quinine over proguanil in the acute attack. With quinine the temperature is usually normal or subnormal by the end of the second day, and the patient feels much better. The action of proguanil is more uncertain, and it is not surprising to see the temperature still up on the third or fourth day. One patient in the present series developed symptoms and signs of cerebral malaria on the third day in hospital while receiving proguanil. Intramuscular quinine produced rapid improvement within twelve hours, and the patient made an uneventful recovery.

The results with mepacrine are as a rule prompt and good, though not as rapid as with quinine. Mepacrine must be given in adequate doses from the start, and it is my practice to give one tablet (0.1 g.) six-hourly for the first two days, sometimes for the first three days, and to follow this by one tablet three times a day for four or five days. My impression is that results with mepacrine are better than with proguanil in the acute attack, and they are slower than with quinine but equally good.

Pamaquin (plasmoquine) in falciparum malaria has a specific action on the sexual forms of the parasites, and is used when these are present. As a routine there is no need for pamaquin in the acute attack.

Two more recent antimalarial compounds are chloroquine and camoquin. Both are very effective, and may in time become the treatment of choice in subtertian malaria.

Chloroquine.—The diphosphate is used for oral medication and the dihydrochloride for parenteral administration. Chloroquine diphosphate is given as an initial dose of 1 g., followed by 0.5 g. after six hours. This is usually enough to terminate the acute attack, and then 0.5 g. is given daily for another two days.

Camoquin.—This is also highly effective. Three tablets of 0.2 g. each are given together at the start, and this single dose is curative in most cases. It is good practice to give

a further two tablets three or four days after the initial dose to prevent a relapse, though this additional dose is not commonly needed.

The above doses of chloroquine and camoquin are adult doses, and children and infants are given proportionately less.

Some Interesting Cases

Most of these have been referred to above, but two cases of malarial pneumonia are here included.

Case 1.—An elderly man who had been ill for one week complained of slight headache, had pains all over his body, and felt tired. There was no shivering, no vomiting, and no feverishness. Physical examination, apart from revealing severe anaemia, was entirely negative. He was afebrile, and the spleen was not palpable. He was admitted for investigation, and to my surprise malaria parasites were found in his blood. He was given antimalarial therapy, and remained in hospital ten days. During this time his temperature remained subnormal, and the spleen did not become palpable; also there were no rigors. Quinine followed by pamaquin, and iron preparations for the anaemia, brought about a cure within three months.

Case 2.—A young woman complained on admission of headache, generalized body pains, and feverishness. There were no rigors and no other symptoms. Physical examination, apart from a pyrexia of 100.8° F. (38.2° C.), was entirely negative. Malaria parasites were present in the blood smear, and proguanil therapy was begun. On the fourth day her temperature was 101° F. (38.3° C.), and there was no subjective improvement. No further physical signs developed, and the blood smear was again positive. Examination of the urine and stools showed nothing abnormal. As the patient was not very ill, it was decided to continue the proguanil and await further developments. On the seventh day she was still pyrexial, and parasites, though scanty, were still present in the blood smear. Quinine was then given, since the proguanil had been discontinued after six days. Within 48 hours the temperature was down, and fell by crisis over two days, being normal on the ninth day. The further course was uneventful.

Case 3.—A boy aged 4½ years complained of severe diarrhoea. The stools were loose, though they contained no blood or mucus. The mother said there had been about 20 motions during the preceding 24 hours. The child had vomited once at the onset of the disease; there were no other symptoms. On examination his temperature was 105° F. (40.6° C.), but, apart from some abdominal tenderness, no abnormal physical signs were found. He had been receiving proguanil prophylactically twice a week. Examination of the urine and stools was repeatedly negative, and as a last resort a blood smear was taken. This showed a very heavy falciparum infection. The child responded well to quinine and symptomatic treatment. His spleen became palpable on the third day in hospital. At no time did he have a rigor.

Case 4.—A young woman was admitted as a case of lobar pneumonia, with typical signs of consolidation at the left base. There was no splenomegaly, and she had had only one rigor at the onset of the disease. She had a cough with blood-stained expectoration. She did not respond to sulphadiazine and penicillin, and a blood smear taken on the fourth day showed a falciparum infection. After quinine the pneumonia rapidly resolved.

Case 5.—This woman was a maternity patient, and on the fourth day of the puerperium developed a temperature of 104° F. (40° C.) and a severe dry cough. Consolidation was found in the right mid-zone, and this did not respond to antibiotics. On the sixth day of the puerperium the spleen became palpable, and a blood smear showed falciparum infection. She responded satisfactorily to antimalarial therapy.

Case 6.—A young female was admitted complaining of severe upper abdominal pain, incessant vomiting of blood-stained matter, and headache; there had been one rigor. She had become ill two days before admission. Examination showed a pyrexia of 101° F. (38.3° C.), which rose that evening to 104° F. (40° C.). There was rigidity of the left upper quadrant, with tenderness in the left hypochondrium. No other abnormality was found. The provisional diagnosis was splenitis of unknown aetiology. Examination of the urine and stools was negative, but a blood smear was positive for malaria. It was decided to treat expectantly, and quinine with symptomatic therapy produced a fall of temperature by lysis, beginning on the third day in hospital; she made a complete recovery in eight days.

Conclusions

These can best be summarized in tabular form. The figures in parentheses refer to the incidence of symptoms and signs in the 50 analysed cases.

Symptoms		Signs	
Rigors	Over half (60%)	Pyrexia	Usual (98%)
Headache	Usual (88%)	Splenomegaly	Over half (56%)
Vomiting	Not common (24%)	+Blood smear	Almost all (60%)
Feverishness	Usual (90%)	Herpes febrilis	Unusual (0%)
Generalized pains	Common (72%)		

The cases reviewed include patients of both sexes and all ages, and, though females preponderate, these patients form a fair cross-section of our hospital population.

Summary

The clinical picture of subtertian malaria is discussed. Cerebral malaria is not considered.

The variations in the clinical picture are discussed, and a series of 50 consecutive malaria patients admitted to hospital has been analysed.

Some illustrative cases are described.

I wish to thank Dr. M. L. Freedman, Director of Medical Services, Bechuanaland Protectorate, for permission to publish this article, and for helpful criticisms.

CONGENITAL DIAPHRAGMATIC HERNIA IN SIBLINGS

BY

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True congenital diaphragmatic hernia is a relatively uncommon anomaly, and its occurrence in siblings has been reported only once previously (Mäkelä, 1916). We record here the case of a woman who gave birth to two children, each of whom died from the condition shortly after birth.

Case History

A German woman, then aged 19, was admitted to hospital in 1948 for pre-eclamptic toxaemia and hydramnios necessitating induction of labour at 36 weeks. Forceps delivery was carried out because of maternal distress and the occipito-posterior position of the vertex. The infant, a boy weighing 6 lb. 14 oz. (3.1 kg.), gasped for about twenty minutes after birth, and then died. At necropsy there was a massive left-sided diaphragmatic hernia. The stomach and intestines, from the ileum to the transverse colon, were present in the thorax, together with the spleen and the left lobe of the liver. The left lung was collapsed and there was considerable displacement of the mediastinum to the right. Two-thirds of the liver, the duodenum, the pancreas, and kidneys remained in the abdominal cavity. There were no other congenital defects.

The patient became pregnant for the second time in 1951. She attended the antenatal clinic at 12 weeks, when her

condition was normal. At 25 weeks she was admitted for a few days with unexplained right-sided abdominal pain, which cleared up spontaneously. At 31 weeks she was complaining of vomiting and was mentally depressed, but there was no oedema, albuminuria, or hypertension. At 33 weeks she was admitted with severe vomiting and moderate oedema of the ankles; her blood pressure was 150/110. There was no further vomiting after admission. Her blood pressure at 36 weeks was 140/88; by 38 weeks it had risen to 150/100, and there was marked oedema of the ankles, face, and abdominal wall, but there was no albuminuria at any time.

After a medical induction at 39 weeks, she gave birth to a male child; its condition at first was good, but it rapidly deteriorated about ten minutes after birth, when it became cyanosed and limp. The air passages were cleared, oxygen was administered, and the child was put in an oxygen tent. Eight hours after birth only the feet remained slightly cyanosed; the breathing, however, was rapid and jerky, and there was diminished chest movement with absent air entry anteriorly and posteriorly at the right base, over the right mid-lobe, and in the right axilla. Bubbling rales were heard at both apices, louder on the right. Heart sounds were normal. A diagnosis of collapsed right lower and mid-lobes was made. His condition deteriorated suddenly and he died 19 hours after birth.

Necropsy showed that the body was well nourished. Cyanosis and engorgement of the face and neck and some oedema of the feet were present, but no external congenital anomaly. A massive right-sided diaphragmatic hernia through a large posterior defect in the diaphragm on the right side was found. The small intestine, spleen, ascending colon, right half of the transverse colon, and pancreas were present in the thorax. The greater part of the liver was in the abdominal cavity, but a large lobulated mass of liver tissue was present in the thorax, attached to the main mass by a narrow isthmus of fibrous tissue; the anterior edge of the diaphragmatic defect appeared to have cut into, and partly segregated, this lobule of liver from the remainder of the organ. The right lung was collapsed. The left pleural cavity was normal. The remainder of the liver, the spleen, the kidneys, the left half of the transverse colon, the descending and pelvic colons, and the rectum were in their normal situation. The brain appeared normal. Sections of liver, adrenal, pancreas, and myocardium were normal. Both lungs showed early expansion of the alveoli, especially in the left lung.

Discussion

Severe congenital diaphragmatic hernia is calculated to occur once in 23,000 deliveries, but lesser defects of the diaphragm are more common. Mäkelä (1916) recorded the case of a woman who gave birth to four children, all of whom died during or shortly after delivery. Necropsies on the second and fourth children showed large left-sided diaphragmatic hernias through large defects in the diaphragm. In addition both children had abnormal genitalia, uterus duplex separatus and septate vagina. The latter observation is significant, as the mother also had a uterus unicollis with an extra vestigial horn, but did not have any diaphragmatic lesions. Necropsy was not performed on the first or third child, so that it is only surmised that they, too, may have suffered from congenital diaphragmatic defects because they died in a similar way. In our own case the mother had had no acute infectious disease during pregnancy, and neither she nor her husband had ever been subjected to irradiation. Although there is no known definite history of congenital defects, of this or any other type, in either the mother's or the father's family, it seems likely that these two identical uncommon congenital defects may be due to some inherited genetic trait. Mäkelä's cases seem to support such a possibility.

Andersen (1949) showed that a genetic tendency to diaphragmatic hernia which was present in a stock strain of laboratory rats could be increased by feeding them on a diet deficient in vitamin A, although the mother showed no evidence of vitamin deficiency. He suggested that these defects might be due to the rate of growth of the diaphragm being slowed. Normally the diaphragm closes before the intestines return to the abdominal cavity from the extra-embryonic coelom. If the diaphragm is late in closing, the abdominal contents can pass up into the thorax through the still patent pleuro-peritoneal canal, and the delayed diaphragm is ultimately unable to close. Such a mechanism might apply in the human lesions—a suggestion supported by the lobated appearance of the liver in the second case, as if it had been nipped by the edge of the closing diaphragm, which ultimately became unable to close completely. While alive to the errors inherent in pursuing too closely an analogy between animal results and human cases, we think it significant that, in experimental animals, tendencies towards inherited defects can be unmasked or accentuated by dietary deficiencies. How far such deficiencies could have played a part in our case is not known, though it is likely that the patient lived on a notably deficient diet during puberty and adolescence in Germany. The occurrence of toxaemia and hydramnios in both pregnancies may also be significant.

The true condition of the second child might have been diagnosed in view of the previous history of diaphragmatic hernia, but such an occurrence in successive pregnancies is obviously very rare. Had the condition been in fact diagnosed, it is clear that no surgical treatment, such as that of Belsey and Apley (1949) or of Gardiner (1950), could have been embarked upon. The chances of the patient having a third similarly affected child are unknown; they are probably high. A high-vitamin supplementary diet would be indicated in any subsequent pregnancy in view of Andersen's findings.

Summary

The case is reported of a woman who gave birth to two children each of whom died shortly after delivery with congenital diaphragmatic hernia.

REFERENCES

Andersen, D. H. (1949). *Amer. J. Path.*, **25**, 163.
Belsey, R., and Apley, J. (1949). *Arch. Dis. Childh.*, **24**, 129.
Gardiner, J. (1950). *Anesthesiology*, **11**, 377.
Mäkelä, V. (1916). *Finska LäkSällsk. Handl.*, **58**, 1107.

RECIPROCAL CHANGES IN BLOOD FLOW OF THE LIMBS AND RECTUM DURING GENERAL ANAESTHESIA

BY

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It has been shown by plethysmography (Lynn and Shackman, 1951) that circulatory changes develop in the limbs of patients undergoing surgery under general anaesthesia. The changes begin as soon as anaesthesia is induced, and occur in the skin and muscle tissue of all four limbs. Further studies (Shackman, Graber, and Melrose) have led to an indirect deduction that coincidental and reciprocal changes take place in the splanchnic circulation.

The experiments of Grayson (1951) in unanaesthetized human subjects, showing that cutaneous blood-flow changes are accompanied by "directionally opposed bowel blood-flow changes," has lent emphasis to our observations. We have repeated Grayson's studies, with slight modification, on several patients undergoing operation, and have confirmed that the coincidental and reciprocal change in blood flow that he noted in the limbs and the lower bowel, after reflex heating, occur also during general anaesthesia.

We have recorded the rectal temperature by a copper-constantan thermocouple inserted into the rectum, the skin

temperature by a similar thermocouple attached to the great toe of one foot, and the calf blood flow—representing muscle flow—by a thermostatically controlled water plethysmograph (Barcroft and Edholm, 1943) applied to the same or the contralateral leg.

The chart is typical, and shows that the skin temperature and the calf blood flow both begin to increase as soon as anaesthesia is induced, and there is a corresponding fall in the rectal temperature.

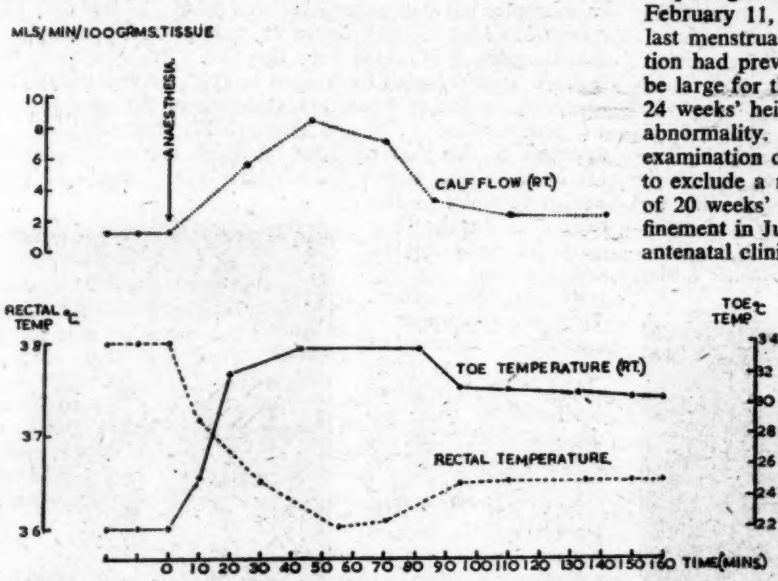

Chart showing effect of anaesthesia (thiopentone, cyclopropane and curare) on calf blood flow, skin temperature of great toe, and rectal temperature

Several minutes, usually about 30, elapse before maximal changes are manifest, but there is throughout the period of observation a close time relationship between the increase in the skin and muscle blood flow and the decrease in bowel blood flow.

These observations have been repeated in 10 patients and have shown a marked degree of constancy.

REFERENCES

Barcroft, H., and Edholm, O. G. (1943). *J. Physiol.*, 102, 5.
Grayson, J. (1951). *British Medical Journal*, 2, 1379.
Lynn, R. B., and Shackman, R. (1951). Ibid., 2, 333.
Shackman, R., Graber, I. G., and Melrose, D. G. In press.

No serious malnutrition was found among Arab refugees from Palestine living in surrounding Arab countries, reports the latest and most extensive investigation carried out jointly by the World Health Organization and the Food and Agriculture Organization of the United Nations. Professor A. G. van Veen, a senior official of F.A.O., and Dr. R. C. Burgess, who heads the nutrition section of W.H.O., spent two weeks this spring visiting refugee camps, feeding centres, hospitals, schools, and clinics in the Lebanon, Syria, Jordan, and the Gaza strip of Egypt. Their joint report agrees generally with the findings of earlier W.H.O. investigations made in the spring of 1950 and 1951 that the nutritional status of the refugees is in many cases better than that of the populations among which they live. They recommend higher rations for refugees in the more exposed camps, and make a series of recommendations to improve the feeding of infants and schoolchildren. Doctors in charge of clinics and hospitals were unanimous that "injudicious feeding was an important primary cause of malnutrition in infants." To remedy this situation the investigators recommend a general extension of the practice at some milk centres to give instructions on infant-feeding to the mothers when they come to obtain their milk. In addition, mothers should be taught the importance of exposing their infants and young children to the sun to prevent rickets.

Medical Memoranda

Full-time Pregnancy Associated with Hydatidiform Mole

CASE REPORT

A primigravida aged 23 attended the antenatal clinic on February 11, 1949, to book for hospital confinement. Her last menstrual period was October 16, 1948, and menstruation had previously been regular. The uterus was found to be large for the period of amenorrhoea, the fundus being at 24 weeks' height, instead of 16 weeks. There was no other abnormality. As there was a family history of twins, *x*-ray examination of the abdomen was carried out on February 16 to exclude a multiple pregnancy. It showed a single foetus of 20 weeks' maturity and the patient was booked for confinement in June instead of July. Thereafter, findings at the antenatal clinic were normal.

She was admitted in labour on June 13, 1949, and had an easy spontaneous delivery of a mature male infant weighing 6 lb. 4 oz. (2,840 g.). Placenta and membranes were expelled complete ten minutes after delivery, and were followed by a fleshy mass about the size of a large lemon. There was no post-partum haemorrhage. The mass proved to be a hydatidiform mole, completely encased in atrophied decidua.

The puerperium was normal. No enlargement of ovaries was noted eight days after delivery, when the Aschheim–Zondek test was negative. On August 27 and December 4 Hogben tests were negative. On the latter day the patient reported that slight vaginal bleeding had occurred, for half an hour only, on one day in October. Lactation was good, the infant being entirely breast-fed. The pelvic organs felt normal.

In April, 1950, the patient failed to report. When she was eventually traced in May she reported that no menstrual periods had occurred since her previous confinement. She thought, however, that she was four months pregnant. Clinical examination showed her to be 26 weeks pregnant, and this was confirmed by *x*-ray examination. The course of the pregnancy was normal, and on August 18 she was delivered of a boy weighing 8 lb. 5 oz. (3,770 g.). This suggests that she had conceived shortly before the last Hogben test on December 4, 1949. The placenta was normal and the puerperium was straightforward. When examined on October 2, 1950, involution was complete.

COMMENT

Hydatidiform degeneration of one of twins with normal development of the other appears to be a rare occurrence. I have been able to trace only two reports of similar cases. In that recorded by Waters and Crunden (1943) the infant was of 36 weeks' maturity. It weighed 4 lb. 12 oz. (2,150 g.) and survived. In that case delivery of the baby was followed by the mole, which was shaped like a disk and resembled a placenta without a cord. The baby's placenta followed spontaneously. This case was followed up for two years, during which time the Aschheim–Zondek test was consistently negative and no pregnancy occurred. The second report, by Favreau and Belanger (1939), was of a case in which the infant, delivered at 36 weeks' maturity, weighed 5 lb. 15 oz. (2,700 g.) and survived. No follow-up is recorded. The case was similar to ours in that the placenta of the first child was delivered normally and was followed by an encapsulated mole, which was the size of a foetal head.

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REFERENCES

Favreau, and Belanger, P. A. (1939). *Bull. Soc. Gynéc. Obstét.*, 28, 179.
Waters, E. G., and Crunden, A. B. (1943). *Amer. J. Obstet. Gynec.*, 46, 299.

Lipoma of the Hypopharynx

Although lipoma is a common tumour, its presence in the pharynx is extremely rare. As a cause of death it is rarer still. These and other unusual features have prompted me to report this case.

CASE REPORT

A single woman aged 58 was found lying in bed early one morning by her brother "with blood and vomit coming from her mouth and a sausage-like bag hanging from her mouth." She was unable to speak to him except in a rambling manner. The general practitioner, who was immediately called, found the patient in the condition described. The tumour was moderately firm and fleshy, and protruded about 4 in. (10 cm.) beyond the lips. It came from the throat and he could not find its attachment. The patient was conscious, agitated, and unable to speak, and had attacks of difficulty in breathing, with some cyanosis. The doctor had never attended her for anything but "coughs and colds," but on inquiry he found that about a year earlier, when her father

FIG. 1.—The patient *post mortem*, with the tumour protruding from the mouth.

died, she had complained of "something coming up in her throat." This, the relatives said, settled immediately, and medical advice was not sought. To the best of the knowledge of the doctor and the relatives she was a healthy woman. The doctor immediately put her in his car to drive her to hospital, but she died on the way in an attack of cyanosis. After death the tumour disappeared.

At necropsy the body was that of a normal well-built, well-nourished middle-aged woman. The tumour was not visible, but on pressing down the lower jaw it gradually emerged from the mouth. By pulling gently with forceps it was brought about 3 in. (7.5 cm.) beyond the lips (Fig. 1). It was pink in colour, with a moderate number of small haemorrhages on the surface. It was cylindrical and had a round end. The surface appeared to be a mucous membrane, and it felt soft and fleshy. It was free except posteriorly, where it curved round into the throat. On opening out the structures the tumour was found to arise from the post-cricoid region of the anterior wall of the pharynx (Fig. 2) by a base largely composed of a double mucous membrane 1¼ in. long and ¼ in. (0.6 cm.) wide. On section the tumour was 6 in. (15 cm.) long and 1½ in. (3.8 cm.) in diameter and did in fact bear a close resemblance to a sausage. A little protuberance of the main tumour was tucked into the laryngeal orifice and partly obstructed it. On section the tumour was found to be composed of fat intersected by fine fibrous strands, with a surface covering of mucous membrane. Histologically it was a simple lipoma. The remainder of the body showed no abnormality save signs of asphyxia.

It is presumed that the tumour had been growing slowly for some considerable time and gradually extended down into the oesophagus. On the morning in question she vomited and brought it up into her mouth and actually out of it. The more she strained to get rid of it the more her cyanosis increased.

COMMENT

The site of the tumour was anatomically the anterior wall of the pharynx, but, because of the continuity and similar form of the oesophagus in this region, lipomata of these structures can be considered together. Most textbooks state that lipomata of the pharynx and oesophagus occur but are rare. Adair *et al.* (1932), in their paper on 352 lipomata, do not mention one in this site. Willis (1948) does not quote an example, but Adams and Hoover (1945), in a review of cases from 1712 to 1943, found 91 cases of benign oesophageal tumours, 5 of which were lipomata. The first appears to have been reported by Vinson in 1922. Almost without exception, so far as I can find, lipomata of the oesophagus are pedunculated. Figi and Hunt (1927) give a list of 35 lipomata of the pharynx, four of which are pedunculated. Lipomata of the larynx are similarly rare. Many of the benign tumours in this region besides the lipomata are pedunculated, and the final diagnosis rests on the section. They are commoner in men than in women and occur more often in the elderly. The symptoms produced by these pedunculated tumours are few, the commonest being the vomiting of a tumour into the mouth. On finding that he cannot rid himself of it the patient swallows it again. Dysphagia is rare, and sudden death from asphyxia has occurred on few occasions. Sometimes there are no symptoms and the condition is found accidentally at post mortem examination.

FIG. 2.—The pharynx and oesophagus opened. The tumour fell back into this position just below the epiglottis and extending down the oesophagus.

Another point noticed while reading some of these cases is that the anterior post-cricoid region is sometimes regarded as larynx, sometimes as pharynx, and sometimes as oesophagus. To my mind this is a pharyngeal tumour, and to give it a more specific site I have called it hypopharyngeal.

I wish to thank Mr. O. Thompson Smith, H.M. Coroner for Colchester, for permission to publish this case. The photographs were taken by West End Studios Ltd., Colchester.

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REFERENCES

Adair, F. E., Pack, G. T., and Farrior, J. H. (1932). *Amer. J. Cancer*, 16, 1104.
Adams, R., and Hoover, W. B. (1945). *J. thorac. Surg.*, 14, 279.
Figi, F. A., and Hunt, V. C. (1927). *Surg. Clin. N. Amer.*, 7, 1531.
Vinson, P. P. (1922). *J. Amer. med. Ass.*, 78, 801.
Willis, R. A. (1948). *Pathology of Tumours*. London.

Dr. Dane G. Prugh, psychologist at the Children's Medical Centre, Harvard University Medical School, told the American Academy of Paediatrics that more flexible visiting hours for parents had proved helpful in preventing emotional problems for children in hospital (*New York Times*, May 24). He wanted parents to take over part of the daily care of their children where surgical treatment was not involved. Experiments had shown that in children from 2 to 12 years of age those receiving routine hospital care, and only one weekly visit from their parents, were less well adjusted than those whose parents visited them frequently. These children were also given advance explanations of all medical treatment they received, and group play was organized for them.

Reviews

THORACIC MEDICINE

Lung Abscess. By R. C. Brock, M.S., F.R.C.S., F.A.C.S. (Pp. 197; 60 figures. £1 15s.) Oxford: Blackwell Scientific Publications.

Those who are acquainted with *The Anatomy of the Bronchial Tree* will welcome this new work by the same author, and at the outset let the highest praise be given to the production and quality of nearly all the illustrations. Mr. Brock has already published a number of articles on this subject, and has now brought together and collated his experience of nearly 500 cases.

In the earlier chapters he describes clearly the important part played by gravity in the site or location of a lung abscess and shows the pathological changes that occur in their varying and alarming forms. The author is at pains to insist on the potential gravity of the condition in every case, and urges a much more vigilant attitude in control than is often accepted. An additional contribution that he makes is the need for establishing an aetiological factor, and where a specific organism is recognized a clinical entity can sometimes be built up; this is particularly so in the case of staphylococcal and Friedländer's bacillus abscesses, which he discusses admirably in two short chapters.

The one thing that is missing perhaps is sufficient differentiation between the majority of abscesses encountered seven or eight years ago and those seen at the present time. Chemotherapy has undoubtedly played a large part in prevention and in the actual course of the condition; indeed, someone accustomed to the old and appalling type of abscesses might well be surprised at the much more benign behaviour usually seen at the present time.

In the discussion on treatment the author writes at some length on external drainage and excision. These methods were undoubtedly of great importance, but now they are required only on rare occasions—which is possible only so long as an active expectant treatment is undertaken. This implies, as Mr. Brock rightly suggests, most careful observation and the use of antibiotics, though the reader might feel that the dose of one million units of penicillin a day for three weeks would hardly meet the requirements of the massive-dose system that some writers have found so effective in reducing the need for surgery.

This monograph makes a valuable contribution to the literature of thoracic medicine in its widest sense. Mr. Brock has added his considerable experience to the study of this complex subject and has given in a clear if somewhat dogmatic style the most comprehensive account of lung abscess yet published. As a footnote, might one ask if it is too much to hope that the term "creepage" has gained only a temporary foothold in medical literature?

T. HOLMES SELLORS.

CONGENITAL DISLOCATION OF HIP

Congenital Dislocation of the Hip. By Julius Hass, M.D. (Pp. 398; 174 illustrations. £4 10s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952.

This book is the result of Dr. Hass's experience of some 2,000 cases of congenital dislocation of the hip, first at the Vienna Clinic in succession to the famous Adolf Lorenz, and latterly in New York. Such an experience and background gives great weight to the views of the author, which, as might be expected, closely follow the lines originated by his illustrious senior.

Dr. Hass gives short summaries of the different views that have been held on the pathology and treatment of this condition, the variety of which is indicated by 70 pages of bibliography. He himself considers that the hip is not dislocated at birth but merely has a tendency to dislocation owing to imperfect development; and that soon after birth the head of the femur leaves the acetabulum, going into an anterior subluxation, whence it passes in some unexplained way to the generally recognized posterior superior position. He then gives a number of signs for diagnosis in the earliest possible stages: the low position of the knee with the femur upright and the child on its back, the limitation of abduction, the "telescoping" of the head of the femur, the snapping of the joint on manipulation, and the *x*-ray appearances. He does not remark that all of these are tests of dislocation, and a posterior dislocation at that. In order to maintain his view that the joint is not dislocated at birth, he has to ascribe the limitation of abduction invariably present to muscular imbalance rather than to an obvious mechanical lock due to the posterior position of the head; and this although the limitation persists under full anaesthesia.

Throughout the book he makes an important distinction, which should be more widely recognized, between the "typical," or straightforward, cases and what he calls the "teratological" ones—those in which the child has other marked abnormalities. Most of these children are "compression babies," and Dr. Hass allows a mechanical element in the causation of their dislocations. He points out that because so many of these teratological cases die early there are vast numbers of reports on their pathology; while the neonatal anatomy of the far more important and numerous "typical" cases is almost unexplored. The only statement he quotes about the position of the head in a dissection of one of the latter class is that it lay on the posterior lip of the acetabulum, but he makes no comment on this.

As to treatment, this is on the lines of manipulation and immobilization taught by Lorenz; there is no mention of the very recent suggestion that controlled movement may be allowed with benefit almost from the start. Dr. Hass is strongly against open operations either as a routine or on the reading of arthrograms without a trial of closed reduction.

The writing of the book is hardly worthy of the experience and knowledge of the author; no one should pass such a sentence as, "Thereafter the thigh is abducted and passes into the socket" (p. 196); or, "Anterior luxation is probably most often a subluxation—i.e., the femoral head is in process of mounting the posterior superior rim of the socket" (p. 54). Fig. 50 is printed upside down, and among minor errors my own name has two different mis-spellings. In a book of the extremely high price of this one proof-reading should really be more efficient.

DENIS BROWNE.

INTRODUCTION TO E.C.G.

Clinical Unipolar Electrocardiography. By Bernard S. Lipman, A.B., M.D., and Edward Massie, A.B., M.D., F.A.C.P. (Pp. 232; 191 figures. $5.) Chicago: The Year-book Publishers, Inc. 1951.

This book is an excellent introduction to the modern use of the cardiograph, which is in the detection and localization of myocardial disease. The authors make no attempt to solve the problems of the arrhythmias.

They approach the subject with the usual physiological account, which is clearly done. They then go on to show how the position of the heart affects the appearances of the various leads: from the unipolar limb leads they pass logically to the bipolar. Ventricular enlargement is well discussed, and the diagrams here are some of the clearest we have seen anywhere. At times the statements are rather too dogmatic: it is doubtful whether, as in Fig. 48, one can really distinguish between left ventricular strain and left ventricular hypertrophy. The more debatable questions of right ventricular hypertrophy are somewhat obscure. The chapter on bundle branch block has many good points. The section on myocardial infarction is probably the best of all. The interpretation of the various cardiographic phases is on the usual modern lines and is described clearly. The diagrams are easy to understand and link up well with the pathological processes.

Throughout the book the reader is logically referred to the physiological facts of depolarization and repolarization; where possible the authors give reasons and conclusions worked out from them. By this means the beginner learns how to solve curves by intelligent deduction and not by memorizing patterns. Such a book may be didactic, but it is easy to follow, and sound. It can be fully recommended to anyone starting this study, and also to those already started who need something to clarify their ideas. Clinical comments are often sound and useful. The diagrams in the text are simple and clear: they may be compared with a large collection of good typical records at the end of the book. Only V leads from the praecordium are shown. There is an adequate bibliography.

TERENCE EAST.

MODERN ALLERGY

Somatic and Psychiatric Treatment of Asthma. Edited by Harold A. Abramson, M.D. (Pp. 752; 90 figures. £4 4s.) London: Baillière, Tindall and Cox. 1951.

From the title of this book and from the preface one would have expected to find a full account of the psychological factors involved in the treatment of asthma. In fact only 77 pages out of a total of 751 deal with this aspect of the subject, and even then a discussion of "maternal rejection" forms the thesis of the greater portion of these pages.

However, when the book is examined as a whole it must be considered as one of the best books on the subject at present available. The short chapter by Boen Swinny on "Specific Treatment in General" is a wise and practical one and should be read by all allergists. His "house-dust precautions" are sensible and attainable by the average patient—a very important point in these times and one that is unfortunately overlooked in most textbooks and writings on the subject. It is useless to give instructions which cannot or will not be carried out by the patient. The reviewer knows of one large asthma clinic at which the dust-sensitive patient is presented with a sheet of instructions which he must follow. Two of these instructions are that every rug and carpet must be removed from the *whole* house and that all wallpaper should be stripped from the *whole* house and the walls painted or distempered. Such an ideal is completely unattainable to-day in this country, and such suggestions cannot help the patient to treat with respect other more sensible instructions. Other outstanding chapters are those on animal and experimental allergy, the nature and chemistry of allergens, and the use of aerosols in allergy.

There are 34 contributors to this book, and each has apparently been allowed full scope to put forward his own ideas within the limits of the space available. This has led to considerable unevenness in the chapters and considerable overlapping. Thus the aphorism, "All is not asthma that wheezes," is repeated six times throughout the book, sometimes being approved and as often being denounced.

The format and printing of the book are of exceedingly high standard, although printing errors are unfortunately frequent. Some are irritating—e.g., "Noone unit" for "Noon unit"; others are incomprehensible—e.g., "The date of nutrition of the patient should be noted." However, these are small matters and do not alter the opinion of the reviewer that this is an excellent book and one that, even at the price, should be in the hands of everyone interested in the modern approach to allergy.

C. J. C. BRITTON.

STRESS

Annual Report on Stress. By Hans Selye. (Pp. 511. $14.) Montreal, Canada: Acta Inc., Medical Publishers (5465, Decarie Boulevard).

This book is the first of a series of annual supplements to *The Physiology and Pathology of Exposure to Stress* by the same author (reviewed in the *British Medical Journal* of October 27, 1951, p. 1014). The *Annual Report* is about half the length of the parent volume, while the general arrangement of the text is similar. Part I is on the general physiology and pathology of stress, and includes an amusing and informative account of reviews, criticisms, and approvals that have recently appeared on Selye's general concepts. Part II is on the special physiology and pathology of stress, taking the systems and target organs of the body in turn.

The method of publishing annual supplements to a standard textbook is a useful alternative to that of producing a series of new editions. But for an individual author the labour would appear to be almost prohibitive. It is therefore even more surprising that this volume, which surveys some 3,000 papers that appeared in the 12 months after the publication of *Stress*, was available to the public four months from the date of publication of some of the papers reviewed.

Whether one agrees wholeheartedly or not with Selye's ideas on the "general-adaptation-syndrome" and diseases of adaptation, this book is without doubt a very valuable contribution to the literature on stress and on the physiology of the pituitary and adrenal glands, and it deserves careful consideration by any worker interested in these fields. It is surprisingly up to date, well indexed, and beautifully produced.

G. W. HARRIS.

RADIOGRAPHY OF THE THORAX

Lehrbuch der Röntgendiagnostik. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. Fifth edition. Parts 5 and 6. Innere Organe. (Pp. 436; 522 figures; M. 84; and pp. 544; 507 figures; M. 98.) Stuttgart: Georg Thieme. 1952.

These two volumes are on the radiography of the thorax. In the first volume the various methods used are fully described in their application to the normal thorax. The authors discuss in great detail the abnormalities which occur apart from disease, the precautions to be taken to avoid error, and the use of contrast materials and other technical methods. Important features in the anatomy and physiology of the lungs are well described and clearly illustrated.

A chapter follows on the general pathology of the lungs and shows in detail how various pathological changes affect the radiographic appearances. The authors then consider general conditions such as bronchiectasis, emphysema, and circulatory defects. They give full accounts of pneumoconiosis and other conditions arising from aspiration, and also of pneumonia in its many forms. The most important section of this volume is that on pulmonary tuberculosis. The many and complex conditions which arise are fully and clearly explained, and they are illustrated from such a wealth of material that every class of case can be followed throughout its development.

The second volume opens with a description of tumours of the lung, of the rarer infections, such as actinomycosis, and of such conditions as granulomatosis and invasion by parasites. The authors discuss diseases of the pleura and the various types of pneumothorax, with a special study of those which occur after thoracic operations, and then abnormalities of the diaphragm and of the mediastina. But the chief interest of the volume is in the application of radiography to the study of the heart in action. By simultaneous records we can study the relation of changes of form to the details of the electrocardiogram. By the injection of contrast material the forms of the cardiac cavities and their relation to the blood flow are clearly demonstrated, both in normal and abnormal conditions of the heart's action and of the valves. The whole section forms a study of the heart on original lines, packed with new ideas and plainly the result of most careful work over a long period. It is worthy of close attention.

Admirably arranged and superbly produced, these volumes form a great and valuable addition to our knowledge in fields of medicine the importance of which can scarcely be exaggerated.

HENRY SOUTTAR.

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THE DEMOGRAPHIC REVOLUTION

The Western and the Eastern nations both have populations problems, but their problems are very different. Death rates are falling rapidly in most parts of the world, or, which comes to the same thing, more people are living longer. But in England and Wales, and indeed in most countries of Western Europe, this is no new phenomenon. The expectation of life of a boy born in England in the middle of the eighteenth century was probably less than 30 years. In 1841, when the figure could be calculated more exactly, it was 40 years. In 1945 the expectation had increased to 63 years, and even in the short interval since then it has continued to advance, reaching 66.5 years in 1950. Girls do rather better, and those born in 1950 could expect to live over 71 years.[1]

The three primary factors that determine population size are births, deaths, and migration. The population of this country grew rapidly throughout the eighteenth and nineteenth centuries, during the period of expanding industrialization, but subsequently reduction of births lowered the rate of population growth and, except for recent years, emigration also had its effect. Though our population is still growing—by 4 millions since 1931[2]—this rate of increase is less than it has been since censuses began. Meantime, as we have been frequently reminded, the age structure of our population has greatly altered, and we are rapidly becoming a nation of few children and many old people. The proportion of persons aged over 65 has more than doubled since the beginning of the century, and the trend continues. What this means in relation to the national economy has been repeatedly stressed—more elderly retired people to be supported by the productive efforts of relatively fewer people of working ages. What it means in relation to medical practice is also well realized—less paediatrics and more geriatrics; fewer tonsils and more prostates; a decline in the proportion of childhood ailments requiring prevention or treatment and an increase in the chronic degenerative processes of the aged. There will be a large, and quite easily calculable, overall increase in sickness and incapacity rates, for elderly people suffer incapacitating sickness much more than the young[3]; and there will be increasing demands for medical advice, and for long-stay hospital and other accommodation for chronic sufferers from the physical and mental infirmities of old age.

England is not alone in having reached this stage of the demographic revolution; most Western countries, including the United States of America, are facing or will soon face a similar situation, but the stage reached varies from country to country. The population problem of the Eastern hemisphere and of some other parts of the world is different and more serious. In countries such as India death rates are falling rapidly, as ours did a century or more ago, but birth rates have not yet started to decline and populations are growing at an unprecedented rate. For instance, between 1931 and 1940 India's population increased by some 50 million, or roughly the present total population of the United Kingdom. Last year the World Health Organization issued a report, primarily for the use of medical and public health workers, on the growth of population in the world.[4] The figures show that the world population has increased from an estimated 1,552 million in 1900 to 2,378 million in 1949, or by more than 50%. The population of North and South America increased by 170 million, more than half of this in South America, while that of Asia increased by 415 million —of which India contributed 138 million and China 106 million. Compared with such figures the increases of a few millions here and there in most European countries are trivial, though Russia's advance from 126 to 200 million can hardly be described as such.

A further report from the World Health Organization[5] examines the influence of the decline in mortality on growth of population during the first half of this century in so far as the influence of mortality can be separated off from that of fertility and migration. In England and Wales 7.8 million out of a total population increase of 11.3 million between 1901 and 1946 could be accounted for by our lengthening span of life; and in Scotland the figure was 1.1 million out of a total increase of 1.7 million. Incidentally, England and Wales and Scotland both lost just over a million persons as the result of war casualties and emigration (with emigration from Scotland into England presumably included). A group of twelve European countries, including Britain, gained some 30 million of population between 1900 and 1945 as the result of reduced mortality. Death rates in Australia, Canada, and South Africa (white population) have declined by some 30% in the past 30 or 40 years; and in the United States by 50% since

[1] The Registrar General's Quarterly Return for England and Wales, 1952, No. 412 (4th Qtr. 1951), Appendix A, H.M.S.O., London.
[2] Census of England and Wales, 1951; Preliminary Report, H.M.S.O., London.
[3] Stocks, P., *Sickness in the Population of England and Wales, 1944-47*, 1949, H.M.S.O., London.
[4] Swaroop, S., *Epidem. vital Statist. Rep.*, 1951, **4**, 162.
[5] Kannisto, V., and Pascua, M., ibid., 1952, **5**, 191.
[6] Palmer, W. L., *J. Amer. med. Ass.*, 1951, **147**, 1187.

1900, which means a saving of about 1½ million lives each year. In several South American countries death rates are lower by a third. In India the reduction in the official death rate from 33 to 18 per 1,000 means a saving of 5½ million lives each year. Unfortunately, in many parts of the world—China, for example—even the simplest mortality statistics are lacking, and therefore it is impossible to estimate accurately the decline in mortality and to determine to what extent the population has increased as a consequence.

Although we in Britain have our population problem and are far from being in full agreement about how it should be solved, our problem differs in character and degree from those of the less developed territories that are just entering the early phases of demographic revolution. Any risk of gross overpopulation in this country has been countered by our lowered birth rate; and eventually falling birth rates will prevent further population increases in Asia and elsewhere. But in the meantime—if the sequence of demographic events in Western society is repeated in Asia—a continuing rapid increase in population during the interim period is to be expected, and this in countries which, unlike nineteenth-century Europe, are already heavily overpopulated. In these countries, where food is already insufficient, further rapid population increase is a grave threat to human comfort and happiness. The magnitude of the crises developing in these areas cannot be exaggerated.*

Nowadays medical advances spread more quickly throughout the world than social and economic progress. The effect of this is to create problems in underdeveloped countries that have so often been solved in the past by famine, pestilence, and war. There would seem to be only two other ways of weathering the storm that is gathering over the large land masses of Asia—limitation of the size of families and the provision of enough food in a world which is short of the "staff of life." The crusading zeal of Lord Boyd-Orr has done much to waken us to the facts and to stir people to action. With more mouths to feed there must be more food. How to do this is largely a political and economic problem. But it is also medical, for the doctor sees in his patients the consequences of malnutrition and starvation. If it is part of the doctor's job to promote health—as it is—then the proper nutrition of his patients should be his first concern. The spacing of children in families by birth control as a method of keeping the human farmyard from being overstocked is a second way of dealing with the problem of overpopulation. But here the difficulties are great. The subject is controversial, the roots of the controversy often lying in deeply held religious belief, or in superstition, or in widely varying social customs. The advance of medical and sanitary science has thrown up as many problems as it has solved—and they are world-wide. As practising biologists medical men cannot stand by on one side and say it is no concern of theirs.

WHAT IS AN ANTIBIOTIC?

That the bacteriologist, who concerns himself usually with the smallest of living things, should have had some of his attentions diverted to the largest is one of the stranger consequences of modern developments in microbiology. The spectacle of a laboratory worker faced with the necessity of felling a specimen of the largest tree in the world, the Californian redwood, or even a common oak, in order to make an extract of it and find out whether it contains an "antibiotic" is not completely fanciful. It is true that in examining trees he has usually contented himself with sawdust from them—for example, that of *Pinus sylvestris*, the Scotch fir, yields pinosylvine, a substance of known chemical composition with a wide range of antibacterial and antifungal activity. But it is a fact that almost every known species of plant, from algae and lichens through every flower, shrub, and weed with which the gardener is familiar to the most majestic of trees, has now been examined in this way. The first complete record of the results of this survey is to be found *inter alia* in *A Dictionary of Antibiosis*, by Leonard Karel and Elizabeth S. Roach.[1] This describes in alphabetical order not only every known antibiotic but every plant or other creature in which they have been sought. Other creatures include *Oncopeltus fasciatus*, the large milkweed bug, the blood of which is alleged to contain an antibacterial substance, and *Apis mellifica*, the honey bee, the blood of which does *not* contain "insecticin," an antibacterial substance found in certain silkworm moths. Among familiar plants one learns with a tinge of regret that no antibiotic activity has been detected in extracts of numerous varieties of crocus, cypress, cucumber, delphinium, hyacinth, iris, or primula. On the other hand, most tulips and roses, and a few passion flowers, magnolias, lilies, gentians, and dahlias, yield active extracts. The seeds of wallflowers contain cheiroline, an extensively studied substance inhibitory to many fungi, but *Viburnum carlesii*, despite the scent with which it delights us in April, is said to be totally inactive.

One object of this survey has been to discover some chemotherapeutic basis for the alleged healing properties of herbal remedies, including not only those used in the Middle Ages and in remote parts of the world but even some of the more peculiar tinctures in the fairly recent pharmacopoeias of civilized countries. From this point of view the results have been singularly disappointing, but the simple tests applied

[1] Published by the Columbia University Press, New York.

may possibly have overlooked some useful action. It has been a common practice in extensive surveys to test extracts only against *Staph. aureus* and *Bact. coli*; it is conceivable, if unlikely, that an extract of some innocent plant to which these bacteria are quite indifferent might have a powerful action on tubercle bacilli or viruses. Moreover, activity may be confined to a particular part of the plant, or vary with the stage of its growth. Nevertheless the fact remains that the only true chemotherapeutic agents which have so far been obtained from higher plants are alkaloids, and their discovery antedates the present efforts by generations. In this connexion it is odd that this book should list *Dichroa febrifuga*, the alkaloid from which, dichroine, is described as effective in malaria, yet mention neither quinine nor emetine. Are these antibiotics, or are they not? The definition of the term given in the preface is "a substance derivable from living organisms and capable of adversely modifying the vital functions of specific micro-organisms." According to this, the human body itself is quite a considerable source of antibiotics: that lysozyme should so be regarded is reasonable, but a definition which plainly includes gastric acid and serum antibodies is questionable. Surely a distinction should be made in the plant kingdom between substances "capable of" adversely affecting micro-organisms and those which actually do so in nature. The products of certain bacteria and fungi undoubtedly antagonize the growth of other species with benefit to those forming them. Possibly essential oils and other substances formed by plants enable them to resist attack by bacteria and moulds, and to this extent they qualify for the description. Otherwise the use of the term seems to call for some restriction. It is logical to regard antibiosis as the opposite of symbiosis, and this implies a naturally observed relationship.

We should nevertheless be grateful to Karel and Roach for having adopted a wider definition, since the result is a work of reference full of interest and invaluable to the microbiologist. The items in it, which number roughly 15,000, include not only antibiotics themselves and species forming them but species and diseases susceptible to them. As between these different categories there is an admirable system of cross-references, and the bibliography, which gives titles, occupies 55 pages. The information given about the more important antibiotics is extensive, although compressed into little space. The book will be particularly useful to anyone who thinks he may have made a discovery in this field: it is easily possible to verify in a few minutes that a substance formed by a certain organism and acting on certain others has already been described, and the references are there to enable the inquirer to get details. This is not so rare or unimportant a use as it may seem, for what bacteriologist does not from time to time find a mixed culture in which something exciting seems to be happening?

BEVAN VERSUS SPENS

It was recently observed that the late Government accepted the Spens recommendations for the remuneration of general practitioners and consultants and specialists in a fit of absentmindedness. Now in a written reply to Mr. Tom Reid, M.P., Labour Member for Swindon, Mr. Aneurin Bevan is preparing, so it would seem, to put the Spens reports into the discard, to use a phrase of one of his predecessors. This is what he is reported to have written to Mr. Reid[1]: "On the basis of this report an immediate increase in capitation was provided and I negotiated with the B.M.A. the conditions under which the doctors eventually entered the National Health Service." The medical profession entered the National Health Service in 1948 on the clear understanding that the terms of service could be immediately discussed. At the A.R.M. in Harrogate in 1949 the Chairman of Council, Dr. H. Guy Dain,[2] said: "At the end of a year we find that the Government is not even yet prepared to agree the terms of service of consultants and specialists in our hospitals, and the final remuneration of general practitioners is not yet determined. . . . We assumed on the statements given to us before we accepted the Service that our entry into the Service was conditional on the establishment of a Whitley machinery by which our terms could always be discussed and which would be backed by arbitration in the event of disagreement. Under no other conditions could we have accepted service."

In his statement last week Mr. Bevan went on to say this: "It is true to say that the B.M.A. always contended that I had not fully implemented the Spens report. I, however, took the opposite view, and, with the establishment of the National Health Service and the entry of the doctors into it, I said that, in my opinion, the Spens report was finished with." This is a most ominous statement and so far we have been unable to find any record that would support Mr. Bevan's assertion. If the Labour Government were to return to power it is not impossible that a future Minister of Health will seize upon this statement in an obscure newspaper as evidence of the policy laid down by a former Labour Minister of Health. It is therefore essential that Mr. Bevan should give the profession an exact reference to his alleged statement that "the Spens report was finished with." That his successor, Mr. Marquand, did not share his view is clear from the terms of reference of the Adjudicator he agreed with the B.M.A.: "To determine the size of the Central Pool . . . in order to give effect to the recommendations of the Spens Committee." It was on the strength of the recommendations of the Spens report that the medical profession with much reluctance and hesitation agreed

[1] *Evening Advertiser*, June 2, 1952.
[2] *Supplement to British Medical Journal*, 1949, 2, 2.

to enter the National Health Service. If any Government were to try to shift its ground—except in full agreement with the profession—then a situation would arise in which there would be no alternative except withdrawal from service.

THE DANGER OF AMIDOPYRINE

Agranulocytosis is one of the most serious manifestations of drug idiosyncrasy. Dunlop and Rolland[1] encountered this complication in 2% of a series of 200 cases of thyrotoxicosis treated with thiouracil or methyl thiouracil. The long list of drugs which may induce acute granulocytopenia now includes troxidone, chloramphenicol, and "diparcol." The use of any of these drugs is a calculated risk, justifiable only if the drug has a clear therapeutic advantage over more innocuous substitutes. Most physicians would think it wrong to withhold the benefits of troxidone from a child suffering from incapacitating petit mal simply because there was a 1 in 100 chance that the patient might develop agranulocytosis, but they would not feel constrained to prescribe for a patient with headache a potentially lethal drug when a wide range of safer analgesics was at their disposal. Amidopyrine became notorious as a cause of agranulocytosis as long ago as 1922, yet cases of agranulocytosis associated with the administration of this drug continue to be reported. Amidopyrine was included in Schedule IV of the Pharmacy and Poisons Act, 1933, and has since been obtainable in this country only on a doctor's prescription. Dr. George Discombe, in a paper appearing elsewhere in this issue, has performed a valuable service by drawing attention to the proprietary preparations containing amidopyrine (combined with a barbiturate) which are sometimes prescribed by practitioners unaware of their composition. Discombe suggests amendments to the existing regulations governing the prescribing and dispensing of amidopyrine which would at least ensure that doctors did not give the drug unwittingly.

Drs. F. Dudley Hart, D. G. Wraith, and E. J. B. Mansell, whose report of a patient with agranulocytosis who recovered after treatment with A.C.T.H. is also published this week, add an important rider to Dr. Discombe's paper: they point out that though amidopyrine itself is not available to the general public, the compound formed by sulphonation of amidopyrine, and sold under the proprietary name "novalgin," is not subject to the provisions of Schedule IV. These authors adduce much circumstantial evidence to incriminate novalgin as the cause of agranulocytosis in the case they describe. Their argument is not impregnable—the patient may have been taking other drugs simultaneously, and the leucocytes in her blood did not fall as quickly as might have been expected when a test dose of this drug was given after full recovery from the acute illness had taken place—but the case against the drug is a strong one.

Even if the goal of preventing amidopyrine-induced agranulocytosis can be reached, the problem of treating the established condition will remain as part of the price to be paid for the potency of modern therapeutic agents. Of the innumerable remedies advocated, only penicillin has stood the tests of time and critical clinical observation. It now appears that A.C.T.H. should bring about a further improvement in the prognosis of acute agranulocytosis due to drug idiosyncrasy. Hart and his colleagues are careful to give a warning that not all cases may respond as remarkably as did the patient under their care, who, in spite of energetic treatment along conventional lines, was *in extremis* when the administration of A.C.T.H. was started. This result, and one at least of the two similar cases reported from North America which Hart and his colleagues quote, fully justify their conclusion that A.C.T.H. (or cortisone) should, at least over a trial period, form a routine addition to the standard treatment of drug-induced agranulocytosis.

[1] *Proc. roy. Soc. Med.*, 1950, **43**, 937.

INFANTS OF DOUBTFUL SEX

The development of the foetus proceeds to quite an advanced state before any obvious differentiation into male or female occurs. It is thus hardly surprising that in a certain number of cases—few, but not so few as is commonly supposed—this differentiation is incomplete and problems of extreme complexity in consequence arise. The advice given for the solution of these problems may make the difference between long years of suffering for parents and child and a life that is often surprisingly happy and contented. It is of first importance that those who have not the necessary knowledge of a most abstruse and complicated subject should refrain from giving early and confident opinions on a case of doubtful sex: ill-considered pronouncements have in the past caused lasting damage. Consultants who work in this field have a lively consciousness of the limits of our present knowledge, and in trying to decide on the most suitable course to be followed they find themselves handicapped, as Mr. D. I. Williams points out in an article at p. 1264, by the lack of a generally accepted classification and nomenclature. He suggests a scheme which has undoubted advantages, not least in doing away with clumsy and vague terms. The description, for instance, of a "female intersex" suggests a definite condition, which is more than can be said for a "female pseudo-hermaphrodite."

In the assessment of the condition and of the prospects for the patient certain apparatus is necessary, together with skill and experience in its use. Urethroscopy is essential in almost all cases, but the number of suitable instruments in existence must be very small. It will be seen that Mr. Williams agrees with the traditional teaching that where real doubt exists the child is better brought up as a boy. A well-known Scottish paediatrician used to add weight to this advice by pointing out the advantage given by masculinity in rewards for equivalent work; but even in the not unlikely event of this reason becoming invalid, it is far less embarrassing for a male not to need to shave than for a female to develop a beard.

The literature of the subject is large and provides a fascinating study in normal and abnormal human nature. It tells of many tragedies and also many comedies of the kind inseparable from a condition whose mere exist-

ence violates many cherished conventions and taboos. It also describes a surprising number of happy marriages in which a partner is of indeterminate or wrong sex: it is a curious point that many such people have particularly cheerful and courageous natures. Among complications in later life there has already been dispute over the validity of a female Olympic record put up by an individual who subsequently "changed sex"; and a judge has recently given the sensible ruling that a similar reversal of status does not invalidate a legacy, the person remaining the same no matter whether regarded as a daughter or a son. It is conceivable that a similar question might arise over the inheritance of a sex-linked title or position, with consequences difficult to foresee.

FOR THOSE THAT HAVE EYES

Some learn best from lectures, some from the printed word, others from pictures, and each mode of understanding brings its own kind of knowledge. The heyday of the spoken word was the Socratic discourse and the mediaeval disputation, the study of rhetoric as a university subject; while the coming of printing meant a change from philosophical speculation and argument to the massing of factual knowledge in encyclopaedia and scientific journal. Now, with photography, the cinema, and television, we are entering the Visual Age. The new social and mental outlooks this implies cannot yet be recognized—it is work for the future historian—but even in the microcosm of medicine the effects are noticeable. Radiography, which is only a specialized form of photography, some time ago revolutionized diagnosis. Sheldon's somatotyping and the study of physique are only possible with the aid of a recording camera, and have produced a new interest in constitutional differences. The many new kinds of microscopes of the last 15 years—phase-contrast, electron, reflecting, *x*-ray, and flying-spot—are already enormously widening the range of scientific observation. Perhaps television, which has already been used to transmit *x*-ray photographs and surgical operations, will revolutionize teaching and consultant practice.

New techniques breed new technicians, and *Medical and Biological Illustration*[1] was founded in part to enable medical photographers and medical artists to discuss with one another the potentialities of their craft. It is good to see that it contains much more than reports on the minutiae of technique. The latest issue, for instance, contains an article[2] on the place of photography in university education, advocating its introduction as a subject of study. This might be valuable if it led to a full investigation of the precise value of films in teaching and an economic estimate of their cost; to a psychological assessment of the extent to which students need visual aids to learning; and to a philosophical understanding of what the emphasis on the visual in education and entertainment will mean. It is not enough to produce clear or beautiful pictures: there must be understanding of what they are supposed to do.

[1] Obtainable quarterly from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, at 12s. 6d. an issue or £2 2s. a year.
[2] Chilton, L. V., *Med. biol. Ill.*, 1952, **2** (No. 2, April), 91.

Meanwhile, as a further step into the Visual Age in medicine, an exhibition of medical illustration opens in the Old Library at B.M.A. House on June 14, and continues till June 28 before moving to the medical school at Manchester University for display from July 7 to 19. It is the work of the medical group (about 250 strong) of the Royal Photographic Society and of the Medical Artists Association, and contains wax models, colour transparencies, composite museum exhibits and teaching panels, as well as medical teaching films. It is a show which demands critical attention from everybody, and not merely the photographer and draughtsman, whether amateur or professional. The medical illustrators are a very active growing body of people. In this Visual Age, are they doing the work that is needed?

THE HONOURS LIST

The medical profession will wish to congratulate all those of their number whose names appear in the Birthday Honours List (see p. 1299). Sir Cecil Wakeley's great services to surgery are recognized in his elevation to the baronetage. In addition to being a busy practising surgeon and President of the Royal College of Surgeons, Sir Cecil is actively associated with the editorship of three periodicals, and since 1919 has been a lecturer in anatomy in the University of London. Dr. Walter Elliot, whom we like to think of first and foremost as a medical man who was once Minister of Health, is made a Companion of Honour in recognition of his many distinguished services to his country. Sir Neil Cantlie, recently Director-General of the Army Medical Services, is made a K.C.B. The honour of Knighthood has been bestowed on Dr. W. E. Hume, F.R.C.P., emeritus professor of medicine in the University of Durham, Dr. E. Laurent, member of executive and legislative councils in Mauritius, and Group Captain H. R. G. Poate, F.R.C.S., honorary consulting surgeon of the Royal Prince Alfred Hospital, Sydney. Among the other honours we may note the C.M.G. bestowed on Dr. Charles Wilcocks, director of the Bureau of Hygiene and Tropical Medicine and editor of its two abstracting journals, and the C.B.E. on Professor Alan Moncrieff, well known as a medical journalist as well as a paediatrician, and on Dr. Ritchie Russell, consulting neurologist and editor of the *Journal of Neurology, Neurosurgery, and Psychiatry*.

HONOUR THE SURGEON

Cambridge University paid a fitting tribute last week to a surgeon who can wield the pen as mightily as the scalpel, and who in learning and oratory sustains the ideal of the medical man as a member of a learned profession. Sir Gordon Gordon-Taylor, welcomed as *chirurgus nulli secundus*, was made a doctor of science (*honoris causa*) on June 5 in company with other distinguished men. The Orator hailed him as a pioneer in the transfusion of blood, as a former orator of the Medical Society of London, and as one who with his hand had relieved the sufferings of many.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

SERUM REACTIONS AND SERUM SENSITIVITY TESTS

BY

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The present low incidence of diphtheria, the mildness of scarlet fever, and the increasing use of sulphonamides and antibiotics in the treatment of acute infections have all combined to reduce the number of patients treated with serum. Many practitioners in consequence have little or no experience in the use of serum, and are unfamiliar with the manifestations of serum allergy. Furthermore, the diversity in the advice given by various authors on the performance and interpretation of the different types of serum "sensitivity tests" has produced much confusion. In order to illustrate this point the following have been abstracted from authoritative publications.

Harries and Mitman,[1]—"Sensitivity is revealed by an intradermal or ophthalmic test. . . . Unfortunately [tests for hypersensitiveness to serum] are not reliable . . . there is no exact parallelism between dermal and general (constitutional) hypersensitiveness." Nevertheless, full descriptions are given. The intradermal test for hypersensitiveness ("the one regarded as most reliable") is discussed in detail. "The ophthalmic or conjunctival test is less sensitive," and "some regard it as inaccurate and dangerous. The scratch test is the safest." In desensitization, or, more correctly, hyposensitization, "clinical practice consists in injecting very small graduated doses of the serum." The intradermal route is advised in testing subjects with a history of previous administration of serum. It is also discussed as a first stage in the special precautions for asthmatics.

Joe.[2]—"Cases which give a history of previous serum administration should have a preliminary injection of 0.5 ml. of the therapeutic serum subcutaneously. If no reaction occurs within half an hour, then the full therapeutic dose should be given by the appropriate route. . . . In cases which present a history of asthma or allied conditions, or of reaction to previous serum administration, the procedure is more elaborate." Methods of giving doses of diluted serum subcutaneously are described. "When the reaction becomes minimal, a small dose should be given intramuscularly, before administering the remainder by this route. . . . To prevent anaphylactic accidents . . . intracutaneous injections or conjunctival instillations of diluted serum" have been used "for the detection of hypersensitive individuals." They are "uncertain guides, and it is doubtful if at present their routine application has any practical advantage."

Ratner.[3]—In determining serum hypersensitivity the scratch test with "concentrated liquid serum may give a dependable reaction. . . . The intracutaneous test is reliable." The ophthalmic or conjunctival test is "valuable." "We may briefly summarize the procedure preliminary to serum administration as follows: (*a*) Detailed history. (*b*) Intracutaneous test. (*c*) Ophthalmic test. (*d*) If the decision is to administer serum, inject a few minims intravenously or subcutaneously before proceeding with the full amount." There is a long discussion about the difficulties and defects of the skin tests, but it is noteworthy that neither the intracutaneous nor the ophthalmic test is dismissed summarily as not worth performing.

Queries and Minor Notes.[4]—While the skin test technique has minimized the incidence of acute reactions, "its limitations in avoiding delayed serum sensitivity are recognized." Reference to the foregoing publication by Ratner is then recommended at the end of the note.

Banks.[5]—If serum is essential . . . in cases of asthma or infantile eczema . . . commence with a dose of 0.1 ml. of 1:100 dilution subcutaneously and proceed with three doses, each increased tenfold over its predecessor, subcutaneously every half-hour. . . . In minor allergic conditions . . . give one injection of 0.25 ml. as a trial dose *subcutaneously* and then wait two hours. This is a test for *general* sensitivity; if there is no general reaction in that time the full dose may be given intramuscularly. Intradermal and conjunctival sensitivity tests are unreliable as test of general sensitivity both in a positive and negative sense."

Parish.[6]—In view of the unreliability of the intradermal and conjunctival reactions, "the safest course is to give a small dose, for example, 0.1 or 0.5 ml. of a 1:10 dilution of serum in sterile saline, by the same route as that which is chosen for the main dose. If no disturbing symptoms appear within half an hour the main injection may then be given very slowly."

Cruickshank.[7]—"Before giving an injection of antiserum . . . the doctor should inquire about a personal history of asthma or hay-fever, particularly from contact with horses, or any family or personal history of allergic disorders. If in doubt an intradermal injection of 0.1 ml. of the serum diluted 1:100 should be given; this will produce a local wheal and erythema reaction in a sensitized person, who may then be partially and temporarily desensitized by repeated small injections of the serum."

It is thus hardly surprising that some doctors take no precautions at all, whereas others perform some form of sensitivity test in cases selected on the basis of the answers to a few stock questions; a few practitioners are unduly cautious and tend to overdo the preliminary testing, even performing tests (such as the intradermal or conjunctival) that are of little practical value as guides to general sensitivity.

The purpose of this article is to endeavour to dispel some of the existing confusion about so-called sensitivity tests. We shall seek to differentiate between (*a*) testing for *local* serum hypersensitiveness—namely, the intradermal injections, conjunctival instillations, scratch tests, etc., with diluted or undiluted serum which are made shortly before the parenteral injection of a main or larger dose of serum; and (*b*) the trial or test doses (used in testing for *general* reaction)—namely, small amounts of serum given subcutaneously or intramuscularly before the administration of larger doses.

In assessing the risks of serum therapy it will be remembered that the complications are infrequent. Serum rashes of all types, often mild and unimportant, have a case incidence of about 5%; and fatal anaphylaxis occurs, according to various authorities, perhaps once in 50,000 to 200,000 administrations of serum. The incidence of serum anaphylaxis may not have been appreciably affected by modern processing, whereas that of serum sickness has been progressively reduced. The latter used to be 40 to 60% with native (crude or unconcentrated) serum; the introduction of ammonium or sodium sulphate concentration reduced it to 20 to 30%, and enzyme treatment or refining reduced it still further to about 5%. The rashes seen nowadays are almost invariably mild and transient, but cannot be entirely eliminated, as the refined product is still a foreign protein preparation to which some persons have become sensitized either naturally or by some artificial means, such as previous injections of serum.

1 Harries, E. H. R., and Mitman, M., *Clinical Practice in Infectious Diseases*, 1951, 4th ed., pp. 35, 43, 47. Livingstone, Edinburgh.
2 Joe, A., *The Acute Infectious Fevers*, 1947, p. 266. Churchill, London.
3 Ratner, B., *Allergy, Anaphylaxis and Immunotherapy*, 1943, pp. 472, 481. Williams and Wilkins Co., Baltimore.
4 Queries and Minor Notes, *J. Amer. med. Ass.*, 1951, 147, 1090.
5 Banks, H. S., *The Common Infectious Diseases*, 1949, p. 75. Arnold, London.
6 Parish, H. J., *Bacterial and Virus Diseases*, 1951, 2nd ed., pp. 21, 88. Livingstone, Edinburgh.
7 Cruickshank, R., *British Medical Journal*, 1952, 1, 212.

Types of Reaction

The following is a short and simplified classification of the reactions which may follow the parenteral administration of serum.

Severe Anaphylactic Shock.—This is an immediate reaction attended with fall in blood pressure (as shown by an imperceptible or very low-tension pulse), dyspnoea, and loss of consciousness, with or without rash or oedema. It comes on typically in a few minutes, or more gradually, and with less intensity from half an hour to two hours after the injection. It may prove fatal if not adequately treated.

Serum Sickness.—This is a syndrome made up of pyrexia, urticaria and other rashes, oedema of the tissues, and joint pains. It occurs in two forms, the common (so-called *delayed*) serum sickness after an interval of seven to twelve days, and the *accelerated* serum sickness after three to four days. (This second form is typically seen in persons who have had a previous serum injection.)

Local Hypersensitivity or Local Anaphylaxis Analogous to the Arthus Phenomenon in Animals.—Marked swelling and induration occur, and, later, sloughing of the skin and subcutaneous tissues, and even of the muscular tissues. The reaction is often the result of faulty management. It is apt to develop when repeated serum injections are being given, particularly when an injection is given while the patient is already suffering from serum sickness due to a previous injection. More than one dose need not be given at the same site, as was formerly believed.

Thermal Reaction.—There is sudden pyrexia with a severe chill or rigor. This is not due to serum hypersensitiveness and occurs mostly after intravenous injection. It is probably caused by pyrogens produced by certain dead bacteria in the processing of certain batches of serum or in various solutions for injection. (The batch numbers, which should always be recorded whenever serum is injected, should be mentioned in a report to the manufacturers, who should be invited to comment on experiences elsewhere.)

The rarer forms of serum reactions such as radiculitis and neuritis are not considered here.

Treatment of Serum Reactions

In the treatment of *anaphylactic shock* (as distinct from prevention, which is discussed later) adrenaline (0.5 to 1 ml. of 1:1,000 solution) should be given at once intramuscularly, and repeated if recovery is not rapid. (If delay is to be avoided—and this point is all-important—a syringe and adrenaline should always be at hand before injections are given). Antihistamine drugs given by intramuscular injection in full doses are also very useful, and are clearly indicated if urticaria or oedema develops. The patient should be kept recumbent, with the head low, and warmed with hot-water bottles and blankets, or by an electric blanket if one is available.

The treatment of *serum sickness* includes good nursing, soothing lotions, such as calamine to the skin, and antihistamine drugs by mouth for one to three days, or, in the more serious cases, by injection. Cortisone has recently been recommended.

Thermal reactions subside in 15 to 20 minutes. The patient should be kept warm until the disturbance is over, and should be given an injection of adrenaline if his pulse flags.

Avoidance of Anaphylaxis

This is the outstanding and fundamental problem. While anaphylaxis may occur in patients who have been injected previously with serum, it is observed more often in those who are intensely sensitive to horse serum and who are being injected for the first time. Many of these patients give a history of asthma or infantile eczema, or, more rarely, some other allergic manifestation, hereditary or acquired. In addition to these two categories, "accidents" have occurred quite unexpectedly in some rare cases with no history of either previous serum administration or allergic diathesis.

The degree of the shock varies directly with both the dose of serum and the rate of absorption into the general circulation, two important points which give a clue to the methods of prevention and control described below.

Sensitivity Tests

Intradermal Tests.—The use of intradermal tests for hypersensitivity of the skin is based on the assumption that the degree of general or constitutional sensitivity can be inferred from the results: this assumption is often quite unsound. It is important that this should be appreciated, for the method is widely used. A usual test is the intradermal injection of 0.2 ml. of a 1:10 or 1:100 dilution of normal horse serum or of the serum to be administered. Sometimes even undiluted serum is used, either as the first dose or as a final intradermal check of safety, before the injection of the main dose by some other route. A large local wheal or redness over a wide area, with some swelling, is sometimes an indication of allergy. But it is useful to recall that any local trauma may produce wheals in some subjects—for example, in dermatographia. Injections of quite innocuous substances may also produce reactions of various kinds. It is therefore not surprising that many experienced clinicians have found the intradermal method unreliable, and have ceased to recommend it. The real value of any test is best estimated by practical experience; by this criterion intradermal testing for sensitivity fails in a high proportion of cases. Some patients have reacted locally to the preliminary test without giving any sign of a general reaction either to a trial or test dose or to the subsequent full dose. On the other hand, patients who showed no local reaction have occasionally developed violent general allergic reactions to the main injection: some have even died, and an attempt has then been made to blame the serum instead of the faulty procedure adopted.

One of us (H. J. P.) has often received letters reporting that undiluted serum, which is still sometimes given intradermally or subcutaneously for sensitivity tests, had caused *local* reaction which led to the withholding of ordinary doses of serum for prophylactic or therapeutic purposes. This matter deserves further consideration, for not only doctors but also their patients have been misled and have refused injections which might well have been life-saving. Apart from the vagueness of some local reactions that are due to trauma, certain flushes observed even when serum is given superficially by the subcutaneous route may be due solely to a cresolic preservative.

Ophthalmic or Conjunctival Tests.—The instillation of a drop of serum, usually diluted 1:10, has been abandoned for several years by most people—but not by all—as a test for general hypersensitivity. Injection of the vessels, itching, and lacrimation are said to constitute a positive reaction. Like the intradermal test, the ophthalmic test is misleading as an indication of general sensitivity. A further disadvantage is the occasional occurrence of severe and dangerous local reaction, sometimes involving swelling of the eyeball and considerable pain.

Scratch Test.—This test is also unreliable, and is of only historical interest. The usual technique was to place on the skin a small drop of serum, or of equal parts of serum and glycerin, and to scratch through the drop with a Hagedorn or other needle. A positive reaction was erythema or an urticarial wheal developing within 30 minutes. This crude method permitted great irregularities in the amount of serum absorbed from the scarified area. When a scratch was made through a drop of 50% glycerin on a second area as a control the accuracy of the test was not materially improved, in spite of the over-confidence of many users.

Trial Doses.—These are preliminary subcutaneous injections of small doses (0.1 ml., or preferably 0.2 ml., of serum or of a serum dilution) which are not given with the purpose of observing a local reaction of any kind. They are meant to be absorbed slowly into the general circulation. We prefer to call them "trial doses" rather than "sensitivity tests" or "desensitizing doses." The conception that a patient can be "desensitized" by numerous graduated injections, either intradermal or subcutaneous, at short intervals, without causing a reaction is probably illusory and in practice probably impossible. The absence of reaction

to any dilution or dose probably means that the patient was never hypersensitive. With the method of preliminary small subcutaneous injections, the patient's *general reaction* to a small dose of serum is first tried before he is given a large dose. The essence of the procedure is to introduce the serum into the general circulation slowly, in small amount, so that should an anaphylactic shock develop it would be almost certainly mild and respond rapidly to the usual therapeutic measures. The method is rational and is not based on any local tissue reaction which may or may not be significant. It has been extensively used by one of us (L. J. M. L.) for over 25 years in daily practice, and also by many colleagues and others. We have found it valuable and safe. It is the method we recommend in cases of suspected serum allergy.

Recommended Procedure

In the ordinary straightforward case two questions must be asked: (1) Has the patient had serum before? and (2) Has he suffered from asthma or infantile eczema? The answer to the second question may be supplemented by further inquiries about other allergic manifestations, hereditary or acquired.

If the answers are negative the required dose of serum may be given intramuscularly for prophylaxis or treatment. (The intravenous route is discussed below.) The patient must be kept under observation for half an hour. If no untoward effects are noted within this period it can be assumed that nothing dangerous will subsequently develop.

If he is sent home the fact should be mentioned that in a few instances some local or general rash may develop, usually seven to ten days after injection. The doctor should ask to be informed of this or any other unusual event. If the patient or his relatives are not forewarned of the possibility of a delayed serum reaction there may be undue alarm in the household and serum may come into some disrepute. We know of instances where permission for the use of tetanus antitoxin has been refused for other patients, in view of the publicity accorded to a generalized serum rash which had developed in a friend or neighbour and about which the doctor knew nothing.

If there is a history of a previous injection of serum, a small trial dose (0.2 ml.) of undiluted serum is injected subcutaneously. A volume of 0.1 ml. is sometimes recommended for this purpose, but is rather small for most syringes in general use to-day. The doctor must keep the patient under observation for half an hour; if no general symptoms develop, the full dose of serum may then be given intramuscularly as required for prophylaxis or treatment. Once again observation for half an hour is necessary. If the patient is sent home at the end of that time he should be warned about the possibility of an accelerated serum reaction, with the appearance of rashes, in about three to four days.

If there is a history of allergic asthma or infantile eczema this will necessarily start a train of other questions, in order to ascertain the severity and frequency of the attacks and their relationship to other forms of allergy in the patient or his family. (From 50 to 70% of allergic patients have an allergic family history.) There may be difficulties in obtaining an accurate history, but the attempt should be made to get an impression of the patient's allergic background. In general, most attention will be paid to asthma in the older subject and to infantile eczema; Britton has pointed out that allergic eczema is commoner below the age of 5 years, and that after this age eczema tends to be replaced by asthma. Of the other allergic disorders, hay-fever, food idiosyncrasies, and eczema other than infantile are much less important, since they are rarely associated with a dangerous degree of sensitivity.

Ideally, asthmatic patients and those with infantile eczema should not receive serum at all, as the risk of anaphylactic shock is considerable. In the case of asthmatics, active immunization with diphtheria and tetanus toxoids is particularly important, in order to obviate the emergency use of any serum. Experience has shown that injection of these prophylactics is rarely associated with untoward reactions in young subjects of allergic diathesis.

If it is necessary, in view of the gravity of the infection, to give serum to asthmatic or eczematous children, the method of the small trial dose, with slow absorption, is absolutely essential. The subcutaneous route of injection is preferred to the intramuscular, the slower absorption from the subcutaneous site and the more superficial location of the serum being obvious advantages. The following scheme of injections is suggested for these cases: (*a*) Give 0.2 ml. of a 1:10 dilution of serum subcutaneously. (*b*) Keep the patient under close observation for half an hour. (*c*) If there is no general reaction, give 0.2 ml. of undiluted serum subcutaneously. (*d*) Once again observe the patient for evidence of general sensitivity for half an hour. If there is no general reaction within half an hour the patient will not subsequently develop really severe anaphylaxis. (*e*) If there is no general reaction, give intramuscularly the full dose of serum required for prophylaxis or treatment. (*f*) Once again keep the patient under close observation for half an hour. (*g*) If he is being sent home he should be warned of the possibility of delayed serum sickness.

In cases of doubtful asthma or allergic diathesis the scheme of injection will depend on the urgency of the illness. If the treatment is not urgent the doctor may proceed as for a known asthmatic. If it is urgent he should follow the method advised for those with a history of a previous injection of serum.

Finally, the question arises whether serum can be given with safety after anaphylaxis has occurred. Fortunately there is seldom any difficulty, provided the doctor waits till the blood pressure is normal and rashes (if any) have subsided after dosage with an antihistamine drug. This should take up to six hours. The trial dose is then repeated, and if there is no reaction after half an hour the full dose may be given.

Intravenous Injection of Serum

The intravenous route of administration merits separate discussion. Although this is by far the most dangerous route for allergic subjects, it may be invaluable for therapeutic purposes, since it ensures that the highest possible concentration of the serum should be immediately available. It saves much time in dealing with an acute infection which may have had all too long a start.

Before the intravenous route is used the preliminary procedures described above for an intramuscular injection should always be carried out. It is neither wise nor safe to give an intravenous injection of serum (whatever the result of the skin-sensitivity test) as a first step in treatment and without a preliminary intramuscular injection that has been tolerated by the patient. Ideally, two hours should elapse between the intramuscular injection and the intravenous injection. In cases of great urgency, however, as in severe diphtheria or tetanus, this interval can and should be shortened, with only a slight risk, but never to less than half an hour. There is no case so urgent that any further reduction of this period would make all the difference in the outcome of the infection. The time of waiting is not wasted; it allows the patient to recover from his journey, and his attendant to get ready the syringe, adrenaline (which should have been available from the start of serum therapy), blankets, hot-water bottles, etc. The delay also allows time for the serum taken straight from the refrigerator to warm up to room temperature; it is not a good plan to warm it in hot water. The doctor should give the injection very slowly, preferably through as fine a needle as possible, and he should be prepared to stop the injection at once if there is any sign of distress. The patient must always be recumbent for the injection and for at least one hour afterwards.

We would reiterate that the trial dose with slow absorption is the main safeguard against dangerous anaphylactic reactions. It may be likened to putting a person first in shallow water to know whether he can swim. When it is

discovered that he can, then only is he plunged into deep water. Serum anaphylaxis can be fatal on rare occasions, but the experienced clinician will generally save his patient. On the other hand, serum sickness may be a troublesome but never a dangerous disease, and there are no fatalities except from ill-conceived treatment.

Conclusion

Whenever serum is injected, whatever the route, the patient should be kept under observation for at least 30 minutes afterwards, with a syringe and adrenaline 1 : 1,000 ready for emergency use.

Intradermal, conjunctival, and scratch tests for the detection of serum sensitivity are unreliable. The small "trial dose," given subcutaneously, is preferable, and should be used in all patients with a previous history of serum injections or allergic conditions.

Serum should never be given intravenously unless a preliminary intramuscular injection has been tolerated and all preparations have been made beforehand for treating shock.

Next Refresher Course Article.—"Clinical Effects of Exposure to Heat and Sunlight," by Professor B. G. Maegraith.

THE PROBLEM OF THE AGED SICK AS SEEN BY THE GENERAL PRACTITIONER*

BY

MORTIMER O'SULLIVAN, M.B., B.Ch.

From the general practitioner's point of view the aged sick are usually those persons who require more or less constant medical supervision and a considerable amount of personal attention. They are mostly visited in their homes, but those who can, even with an effort, attend during surgery hours are encouraged to do so. For the general practitioner there is no clear dividing line between the chronic sick proper and the aged infirm. This classification is of importance to us only when the question arises of removing them from their homes. Before and after they should become the responsibility of either the hospital or the local health authority the general practitioner has usually to look after them for a considerable time.

Speaking as a middle-aged general practitioner, one is thankful that all the aged do not come under one or the other category. Most of the over-seventies are hale and hearty. But when a doctor has worked in the same district for a number of years his patients grow up with him, with the result that the older he gets the more aged sick he has to look after.

In the last quarter of a century the face of medicine has changed. Osler's remark that "pneumonia is the friend of the aged" is no longer true. Since the advent of the antibiotics the chance of death from natural causes has decreased, and at the same time the improvement in anaesthesia and surgery has greatly reduced the risks of operation.

Types of Aged Sick Encountered

As is to be expected, most of the aged sick are suffering from some degenerative process. In my present list of chronic cases I find the majority to be those of cerebral arteriosclerosis or of encephalopathy—patients with severe headaches, mental degeneration, irritability, retinal haemorrhages, senile cataract, transient paralysis, and a condition which, to me, seems to be on the increase, vertigo. The next largest group may be classified as coronary arteriosclerosis and hypertensive failure: this class varies from the impaired myocardium as the result of coronary thrombosis to the senile cardiac asthmatic. Next there are the arthritics—the chronic cases of rheumatoid arthritis and of osteoarthritis, both making their victims house-fast. Cases of chronic bronchitis and of pulmonary heart disease breaking down several times a year are always present. I have four cases of hemiplegia, three of disseminated sclerosis, two of paralysis agitans, and four of other forms of paralysis. There are five cases of inoperable carcinoma, four cases of chronic tuberculosis which require visiting, two cases of heart failure from rheumatic disease, one case of pituitary tumour, and one man with senile prostate who refuses operation and has had to be trained to catheterize himself, with all its attendant sequelae and complications. There are two mental cases, both women, who in spite of their delusions (they have been in hospital many times) make a laudable effort to run their homes but are always a worry. There are two cases of hysteria, in both of which one can produce a hemianaesthesia at will. I find that hysteria in the aged is a not uncommon symptom. Finally there are five senile cases, all over 90, with nothing much wrong except that they are physically and mentally enfeebled.

Reasons for the Problem

Perhaps Job was the first recorded case of a chronic sick person. Certainly there have always been aged sick. The problem has become acute (mainly in the urban areas), principally for the following reasons.

1. *People Live Longer.*—If you survive long enough you are almost certain to get on a chronic sick list. About ten years ago I assisted at an operation for the local removal of a carcinomatous breast in a woman of 96. The operation was necessary because the growth had began to fungate. The patient survived for four years.

2. *Absence of the "Handy Woman."*—A generation ago there were in each of the poorer streets of a district one or two of this type of female. They attended at the time of birth, carrying pails of hot water. They would sit at night with a sick person. The more efficient gave an enema if required, and they finally did the washing and laying out after death. Very many of them were retired "gamps," and, although neither home helps nor nurses, combined the duties of both.

3. *Housing.*—The housing situation to-day reflects directly on the young and indirectly on the old. Gone are the days when the family had means and accommodation to care for aged relatives and servants past the age of service. Few young couples lucky enough to have a house are now able to start married life without having an aged relative thrust on them. As children come along there is no longer enough accommodation for them all; domestic friction arises, and so begins the trail of events which leads to the demand for hospital beds.

4. *Tendency to Avoid Responsibility.*—Because weekly contributions are paid to the State there is a feeling that it is the duty of the State to nurture and nurse, and that the care of the aged is no longer the responsibility of the family.

Home Treatment

I would like here to emphasize—and I think that most general practitioners would agree—that any service dealing with the aged should be so designed as to make it easier

*A paper read to the Middlesex Medical Society at the West Middlesex Hospital, Isleworth, June 14, 1951.

and more practicable to nurse this type of patient in his home rather than to endeavour to increase hospital accommodation. Hospitalization or local authority accommodation solves the problem for the relatives and the general practitioner, but in most cases not for the patient. Old people do not take kindly to removal from their usual surroundings. Many die quickly, and I have known some cases of dementia which resolved themselves on the return of the patients to their homes.

The problem of the aged sick has many aspects: the person may live alone or with another aged person or with relatives, and advice and treatment are influenced by the home conditions and the facilities available. Our problems may be divided into medical and domestic.

Medical Aspects

Occupational Therapy.—Many try to occupy themselves, but many more would benefit from expert training. The bedfast sick patient lives in a world limited by his room. Small events matter a lot, and the completion of a piece of knitting or tapestry is a cause for celebration.

Physiotherapy.—We all know of the long waiting-list at hospital for this branch of treatment, and there is usually a wait in hospital itself before treatment is administered. Is there any possibility of treatment in the home for the odd cases where transport causes distress and pain?

Investigations (*x*-ray examination, E.C.G., blood test, etc.).—One can become stale on a case because of frequent visits and not notice changes in the patient. Investigation at regular intervals would help the general practitioner to assess the patient's condition more accurately.

Foot Clinics.—Many of the aged infirm become the chronic sick and confined to the house because their feet give out. The old-age pensioner cannot afford the fees of a private chiropodist. The establishment of foot clinics would postpone the immobility of the aged.

Minor Problems such as Constipation and Insomnia.—It is very easy for an aged person to get constipated, and once the rectum is overloaded the feeble muscles are no longer able to expel the bolus. The procedure of manual removal (as many of the cases require) is unpleasant for the operator and the patient. To make sure that there is no recurrence the patient often uses aperients too energetically and so becomes incontinent. Not all the aged respond well to narcotics, and it is alarming to find the patient who has been given a sleeping draught mentally confused for the following few days.

Domestic Aspects

Shopping has to be done and food prepared, otherwise the nourishment is going to consist of bread and tea, with sooner or later the symptoms of malnutrition.

Washing of the Patient.—Nearly all old people living alone become dirty. The bathroom is cold or the preparation of the bath (often a zinc bath in the kitchen) is too much trouble. Similar problems are the washing of clothes and bed-linen, the cleaning of rooms, and attention to fires.

Social Intercourse.—Many of these people spend long hours alone. The value of the doctor's visit is only partly medical. The fifteen minutes spent with an old sick person is worth much more than a bottle of medicine.

Finance.—I feel that in some cases the relatives would be prepared to look after and care for an aged sick person if a contribution were made to the family budget. After all, if the patient has to occupy a hospital bed it costs the country about 15 guineas a week. In suitable cases anyone who takes on the arduous duties of nursing an aged sick relative should be compensated. Is it possible for a relative to be appointed a home-help with overtime pay for week-end work?

Suggested Improvements

1. *Admission to Hospitals or Homes During the Family Holiday.*—I think most children are anxious to look after the aged sick parent, but it is the continuity of care which gets the family down, and surely the young family is entitled to expect a little time to itself once a year. I realize the difficulty from the hospital side—once the patient is in hospital the relatives may not be so anxious to have him home.

2. *Supplies of Bed-clothes and Night Attire for the Incontinent Patient.*—An efficient laundry service would help to solve this problem.

3. *Male Nurses.*—While appreciating the very good work done by district nurses (and in our district we are very fortunate), we all know there are certain cases better looked after by men. One male nurse to every three or four female nurses would suffice, and I know from personal experience they could all work well together.

4. *Sick Visiting.*—To visit the sick is one of the corporal works of mercy. There is a great opportunity here for the churches. If more interest were shown in the aged sick there might be a chance of the younger people taking an interest in church affairs. The problem arises, whose duty it is to inform the appropriate vicar. Perhaps the general practitioner is here at fault for not doing so more often. While on this subject I would like to pay tribute to the Darby and Joan homes in our district. A lonely old man died recently, and I was pleased to find two friends from the home turning up to take care of the body and to look after his affairs.

5. *Increase in Number of District Nurses.*—A seasonal increase would be a great help. In the winter of 1950–1 these nurses had not a chance to deal with the number of calls on them. I would like also to make a plea for the provision of some home help for the week-end work.

6. *Priority Hospital Accommodation for Certain Dying Patients.*—I refer to the type of case that is in a coma, that is incontinent, and whose nursing is most distressing for relatives. This state of affairs may go on for weeks. Alternatively, the provision of sitters-in or nurses for night work during acute or terminal illness is suggested.

Conclusion

Finally, the general practitioner has often to deal with the problem that should not be a problem at all. An elderly sick person is put to bed for some minor illness, but when the illness is over the patient refuses to get up, perhaps because it is cold and there is not enough heating in the house. Very soon there is disharmony between the patient and those looking after him. The relatives first demand his admission to hospital, and in a few days the patient makes the same request. The general practitioner points out that the patient is now well and does not require hospital treatment. He is then accused of having a vested interest in keeping the patient out of hospital. Later there is the threat of a letter to the Minister of Health. The only solution to this problem is to send the patient to the out-patient department of the local hospital, where he will be told in no uncertain terms about his condition. He comes home with restored confidence in his relations, and realizes that, after all, his doctor is not the worst in the world. This problem is then solved for another twelve months.

Such are some of the problems which the average general practitioner has to face in dealing with the aged sick. Whatever the future of medicine in this country, the chronic sick and aged infirm will in the main be the responsibility of general practice. It is hard work, often harassing and occasionally satisfying. The few improvements suggested may help to solve the problem.

MEDICAL BIRTHDAY HONOURS

The names of the following members of the medical profession were included in a Birthday Honours List published in *Supplements* to the *London Gazette* on June 5:

Baronetcy

Sir CECIL PEMBREY GREY WAKELEY, K.B.E., C.B., F.R.A.C.S., F.A.C.S. President of the Royal College of Surgeons of England.

Companion of Honour

The Rt. Hon. WALTER ELLIOT ELLIOT, P.C., *M.C.*, D.Sc., M.B., Ch.B., F.R.C.P., F.R.S., M.P. Member of Parliament for Lanark, 1918–23; for Kelvingrove Division, 1924–45; for Scottish Universities, 1946–50; and for Kelvingrove Division since 1950. Minister of Health, 1938–40; Secretary of State for Scotland, 1936–8; Minister of Agriculture and Fisheries, 1932–6. Financial Secretary to the Treasury, 1931–2. For political and public services.

K.C.B. (Military Division)

Sir NEIL CANTLIE, K.B.E., C.B., *M.C.*, M.B., Ch.B., F.R.C.S. Lieutenant-General, late R.A.M.C. (now retired). Late Director-General, Army Medical Services.

Knighthood

WILLIAM ERRINGTON HUME, C.M.G., M.D., F.R.C.P. Emeritus Professor of Medicine in the University of Durham. Lately senior physician, Royal Victoria Infirmary, Newcastle-upon-Tyne.

EDGAR LAURENT, C.M.G., M.D. For public services in Mauritius.

HUGH RAYMOND GUY POATE, M.V.O., M.B., Ch.M., F.R.C.S., F.R.A.C.S., Group Captain, R.A.A.F. Honorary Consulting Surgeon, Royal Prince Alfred Hospital, Sydney, New South Wales.

C.B. (Military Division)

ARNOLD GUY HARSANT, O.B.E., M.D., M.S., F.R.C.S., Major-General, late R.A.M.C. Honorary Surgeon to the Queen.

JAMES MACCONNELL KILPATRICK, O.B.E., M.B., B.Ch., Acting Air Marshal, R.A.F. Director-General of R.A.F. Medical Services. Honorary Physician to the Queen.

THOMAS MADILL, O.B.E., M.B., B.Ch., Surgeon Rear-Admiral. Honorary Physician to the Queen.

C.M.G.

CHARLES WILCOCKS, M.D., F.R.C.P. Director, Bureau of Hygiene and Tropical Diseases, Keppel Street, London, W.C.

C.B.E. (Military Division)

FRANCIS WILFRID PETER DIXON, M.B.E., M.B., B.S., F.R.C.S., F.R.C.S.Ed., D.O., Air Commodore, R.A.F. Honorary Surgeon to the Queen.

ERIC SNOW MCPHAIL, V.R.D., M.B., Ch.B., Surgeon Captain, R.N.Z.N.

JOHN GEORGE MAGUIRE, M.B., B.Ch., Surgeon Captain, R.N.

ALBERT SACHS, M.Sc., M.D., Brigadier (Temporary), late R.A.M.C. Director of Pathology and Consultant Pathologist to the Army.

C.B.E. (Civil Division)

ALDINGTON GEORGE CURPHEY, M.B.E., *M.C.*, E.D., M.D., C.M., Colonel, Jamaica Service Corps. For public services in Jamaica.

WILLIAM ROBERT MACFARLANE DREW, O.B.E., M.B., B.S., F.R.C.P., Colonel (Temporary), R.A.M.C. Lately Professor of Medicine at the Royal Medical College, Bagdad.

JOHN JOSEPH HOLLAND, M.B., F.R.A.C.S., J.P. For public services, especially in connexion with the ambulance service, in Western Australia.

ANDREW BUCHANAN MACDONALD, M.B.E., M.B., Ch.B. Lately Superintendent, Itu Leper Colony, Church of Scotland Mission, Nigeria.

SYDNEY ALAN STORMER MALKIN, M.B., B.S., F.R.C.S., F.R.C.S.Ed. Vice-chairman, Portland Training College for the Disabled.

ALAN AIRD MONCRIEFF, M.D., F.R.C.P. Nuffield Professor of Child Health in the University of London.

WILLIAM RITCHIE RUSSELL, M.D., F.R.C.P., F.R.C.P.Ed. Consultant Neurologist, Ministry of Pensions.

WILLIAM JAMES STUART, M.B., Ch.B., F.R.C.S.Ed. Chairman of the Executive Committee of the Scottish National Blood Transfusion Association. President, Royal College of Surgeons of Edinburgh, 1937–9.

O.B.E. (Military Division)

ANTONY JOHN BARWOOD, M.R.C.S., L.R.C.P., Wing Commander, R.A.F.

EDWIN WILLIAM HAYWARD, F.R.C.S.Ed., Colonel (Temporary), R.A.M.C., R.A.R.O.

DERMOT FRANCIS WALSH, M.B., B.Ch., F.R.C.S.Ed., Surgeon Commander, R.N.

O.B.E. (Civil Division)

LLOYD OSCAR ABEYARATNE, L.M.S. Medical Officer, Hospital for Women and Children, Colombo, Ceylon.

Alderman ALBERT CAMPBELL, L.M.S.S.A. Mayor of Accrington, 1951–2. For public services in Accrington.

GEORGE CHESNEY, M.D., D.P.H. For services as Medical Officer of Health for Poole.

HERBERT EMERSON, *M.C.*, M.B., B.Ch. Senior Medical Officer, Ministry of Pensions.

GEOFFREY JASPER ST. CLAIR FISHER, M.B., Ch.B. Senior Gynaecologist, Auckland Hospital, New Zealand.

WILFRED VIVIAN HOWELLS, M.B., B.Chir. Member of Central Health Services Council.

JOHN JOSEPH LANDERS, M.B., B.Ch. Principal Medical Officer, H.M. Prison Service.

MABEL GORDON LAWSON, M.B., Ch.B. Deputy Chief Nursing Officer, Ministry of Health.

NOEL SPENCER NAIRNE, M.R.C.S., L.R.C.P., Medical Officer, Ministry of Transport.

MAHAPITIYAGE VELIN PETER PEIRIS, M.B., B.S., F.R.C.S. Visiting Surgeon, General Hospital, Colombo, Ceylon.

DENYS HENRI RENÉ VOLLET, M.B., Ch.B. Director of Medical Services, Basutoland.

M.B.E. (Military Division)

KEITH ERNEST GOREY, Lieutenant, R.A.A.M.C.

JOHN LUDLOW WHITMORE, M.R.C.S., L.R.C.P., Major (Temporary), R.A.M.C.

M.B.E. (Civil Division)

JUSTIN AELIAN FERNANDO, L.M.S. Medical practitioner, Colombo, Ceylon.

WILLIAM DAVID STONEY JOHNSTON, M.D., F.R.A.C.S. For services to the community in Nelson, New Zealand.

CAROLINE BAXTER KIBBLE, M.R.C.S., L.R.C.P. Lately temporary Lady Medical Officer, The Malay Regiment, Federation of Malaya.

JOYCE REWCASTLE LUDLOW, M.B., B.S., F.R.C.S. For medical and social welfare work in Nigeria.

GEORGE FELIX RANDEGGER. Medical Adviser to Her Majesty's Embassy and to the British community in Rome.

The honour of Knighthood was conferred also on Ronald Aylmer Fisher, Sc.D., F.R.S., Arthur Balfour Professor of Genetics in the University of Cambridge, and on Bryan Harold Cabot Matthews, C.B.E., Sc.D., F.R.S., Professor of Physiology in the University of Cambridge, for his services to the Air Ministry.

From America come reports of a way to deal with rebel tuberculous patients. A locked isolation unit with accommodation for 26 cases of active or communicable tuberculosis has been established by the board of health of the City of Columbus for patients who refuse treatment (*Ohio St. med. J.*, 1952, **48**, 25). The authors of the paper state that since this was done the numbers of patients discharging themselves from ordinary hospitals has decreased considerably. Patients who have been compulsorily isolated may transfer to other hospitals by undertaking to remain there until officially discharged. In Seattle, Washington, patients who refuse to go into hospital for tuberculosis treatment can be legally forced to do so, according to Dr. Cedric Northrop, Washington tuberculosis control officer (*New York Times*, June 1). They are kept under lock and key for two weeks and then usually transferred to a general ward if they promise to behave. "This drastic method of dealing with recalcitration works," declared Dr. Northrop; "it has not generated a group of embittered patients . . . co-operation is ultimately secured."

Correspondence

Height of Scotsmen

SIR,—We have just completed a survey of the stature of Scotsmen between 18 and 40 years of age. The occupations of the men were noted with the other information, and these have been coded into the Registrar-General's social classes, using his *Classification of Occupations, 1950*. The mean stature of each of these classes has been computed and compared with existing data. A summary of the findings is given below, because they provide additional information on several aspects of the problem of adult stature referred to by Drs. J. V. G. A. Durnin and J. B. de V. Weir (May 10, p. 1006).

The mean stature for the Registrar-General's occupational groups were found to be:

Group 1	(Professional)	68.93 ± 0.37 inches
,, 2	(Intermediate)	67.70 ± 0.14 ,,
,, 3	(Skilled)	66.87 ± 0.07 ,,
,, 4	(Partly skilled)	66.42 ± 0.11 ,,
,, 5	(Unskilled)	66.44 ± 0.10 ,,

These mean adult statures are very similar to comparable means reported by the British Association Survey in 1883, but the mature adult stature is reached now before the 19th year in all the classes. The mean statures for the Shetland Islands, the only completely comparable area in the two surveys, are also not significantly different.

The relationship of age and stature over the period of 18–40 years of age is linear and the regression coefficient relating them is -0.032 ± 0.007 inches per year; this is equivalent to a decrease in stature at the rate of about 1 inch in 30 years. This trend becomes apparent immediately after full stature has been reached and is the same in each social class.

The similarity of the mean statures of comparable groups 70 years ago and now is evidence that the age changes found in this cross-sectional type of survey reflect a process of ageing and not an absolute increase in the mean stature of the young adults—a conclusion which, as the authors point out, will need observations on the same people throughout their working life for confirmation. The reported differences seem nevertheless to be greater than would be expected on the basis of these changes. Thus, after standardizing for age, and making no allowance for the reported systematic error of measuring, the mean stature of the sons is about 0.8 in. taller than their fathers. This difference is statistically significant ($P<0.01$). Unfortunately we have no useful data on women. This change in the stature of students may possibly be related to the finding of different mean statures in the social classes.—We are, etc.,

E. M. B. CLEMENTS,
K. G. PICKETT.

Birmingham.

Growth and Development of Children

SIR,—Professor R. J. A. Berry writes (May 24, p. 1133) that he regrets that English workers do not pay more attention in growth studies to the size and rate of growth of the head. He writes that size of head is indicative of that of the contained brain and "it has long since been established that it is size of brain which counts, not shape." I am interested to know when and where it was established and for what it counts. There is strong evidence (Broom, M. E., *School and Society*, 1932, **36**, 703; Paterson, D. G., *Physique and Intellect*, D. Appleton-Century Co., Inc., New York, 1930) that correlations between head measurement, cranial capacity, and intelligence are uniformly low (of the order of 0.12). Another pitfall is the example of the hydrocephalic child who might be assumed to have a large brain.

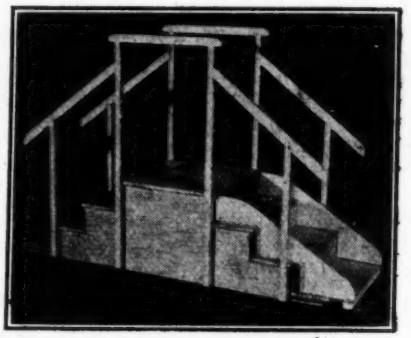
There is so much that one can measure on the growing child, and it is important to discard those measurements which, on all carefully sifted evidence, give results which are not useful in assessing the picture of growth.—I am, etc.,

FRANK FALKNER.

London, W.C.1.

Re-education in Walking

SIR,—Physiotherapy departments have as their aim the restoration of some lost function of a patient, but to be really effective the practical problems of life must be considered during the treatment period. Few of us spend our lives at ground-floor level, so that the patient with a disability affecting one or both legs must have included in his treatment practice in climbing stairs. Some physiotherapy departments make use of a set of wooden steps, whilst others use the ward stairs, but both have disadvantages. The patient who during his treatment starts to climb stairs often needs to put the whole length of his foot on the step, but with the standard steps with a 9-in. (22.9-cm.) tread it is usually impossible. A step with a 12-in. (30.5-cm.) tread would be an advantage during the early stages of training, but the patient should before discharge from hospital be taught to climb stairs of a normal width. The joiners of the hospital have therefore made me an overlay step of 12-in. tread, which slides easily over the standard set of steps and can be easily removed (see photograph).



Physiotherapy time is usually limited, but if a set of parallel bars is placed down the centre of the ward patients can practise walking many times each day. In my wards, where active treatment is given to aged and chronic sick patients, a set of parallel bars 8 ft. (2.2 m.) in length and the same width as the steps is placed down the centre next to them. The bars are easily moved by one nurse to any particular patient, and are regarded most affectionately by the patients.

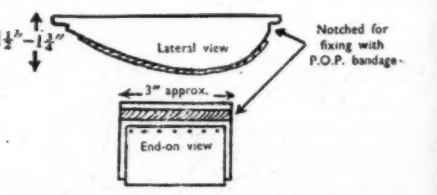
Furniture such as this installed in a ward where patients need re-education in walking will considerably reduce their stay in hospital, since they can use this apparatus over a considerable period each day.—I am, etc.,

J. M. GREENWOOD.

Manchester.

Wooden Heel for Walking Plasters

SIR,—There appears to be little difference mechanically between the Böhler's iron and Dr. Donald Pottinger's heel (March 29, p. 710). Each gives a small walking surface of such low contact area as to facilitate easy slipping, each is a projecting surface neatly designed to trip the patient, each allows the patient to scrape his toes, and each exposes the plantar portion to the weather and allows it to become wet and soggy. Whereas the Böhler iron has a slight tendency to tip the patient forward in his normal direction of motion, Dr. Pottinger's device is so placed that the patient is thrown backwards by the moment of the force acting at the point of attachment; this, I feel, is a questionable improvement.



The actual position of application tends slightly to crack the plaster in front of the ankle-joint, and, being constructed from wood, I doubt very much its ability to survive the normal minimum life of a correctly applied plaster (three to four weeks).

There appear to be two favourable points about the "Pottinger heel." (1) Its major weight-bearing axis being

at right angles to the direction of motion does prevent rotation. (2) The upthrust tends to help the position of leg to foot to maintain its general relationship—that is, 90 degrees. The first is, I fear, cancelled by the obvious difficulty in walking on such a small surface, while the second is neutralized in that this should never be necessary in a correctly applied plaster.

I would suggest that interested readers use instead the highly satisfactory wooden rocker. This can easily be made in assorted sizes and shod with leather or fibre impregnated with rubber. It is easy to affix; if properly applied it rarely works loose; it is comfortable; can be removed, retreaded, and used again. Its best feature is that it permits a smooth natural walking motion and enables the walking patient to return to his routine daily work virtually unimpeded by his plaster. There is usually no need to raise the opposite shoe, and even children tolerate it and are as active as ever. It is widely used, highly efficient, and of proved value both in Service and civilian orthopaedics.—I am, etc.,

H.M.S. Terror. C. R. MAY,
Surgeon Lieutenant, Royal Navy.

Theory of Cancer Treatment

SIR,—The present theory of cancer treatment considers only two factors, the surgeon's knife (or rays) and the cancer cell; it has no room for the natural history of cancer, as Dr. Frank Riggall observes in his interesting letter (May 10, p. 1029). Although we know a great deal about the natural healing tendency which causes a malignant tumour to become stationary for years and perhaps to regress of its own accord, we have not been able to digest this knowledge and to absorb it into our rationale of treatment. The reason for this is rather startling. Our treatment of cancer by radical surgery and radical radiotherapy is not based on facts and logic, but on faith which has become a dogma.

The rationale of cancer surgery rests on the *belief* that a true analogy exists between malignant growth and infectious disease, that the "virulent" cancer cell is the real villain, and that its destruction at all costs and at all points, in one session, is the surgeon's proper answer to the problem.

The rationale of radiotherapy rests on an analogy with the principle of "Therapia magna sterilisans"—the *assumption* a priori (before all experience) that *x* rays kill cancer cells and leave normal cells undamaged.

Yet all pathologists are agreed that malignant growth is not an infectious disease, but a process of faulty regeneration and differentiation; that the cause of cancer is not the cancer cell, but the breakdown of the inherent "co-ordinating mechanism" (Barnard) controlling normal growth and repair. The specific "cancer" cell is a myth. In the various parts of the body cells can be found which resemble in every respect those which are found in tumours. Nor are these so-called cancer cells "aggressive"; as a matter of fact, they are frail and vulnerable "displaced persons," unable to grow by themselves; they can only do so with the help and kind permission of the *stroma* which the organism provides. Stray cells from the tumour get into the lymph and blood stream in the same manner as other foreign bodies, dead or damaged cells, are taken into this drainage system; and if they get there, they are destroyed. Tumour embolism is not tumour metastasis (Willis).

The local defence processes accompanying established growth have been well studied. Inflammatory reaction is a highly significant feature of malignant tumour growth. Ewing holds that a well-marked reaction indicates a pronounced capacity to limit the growth. Mayo called the stroma of a cancerous growth "the measure of Nature's resistance." It is the same stroma which first encourages and nourishes the pseudo-regenerative process that eventually mobilizes its mesenchymal forces in an attempt at removing the strange cell masses from its territory. The reason that these attempts are so feeble is that the tumour cells are not strange enough to rouse the defensive mechanism to full activity. This goes to show that in the natural history of cancer the stroma is much more important than the cancer cell. If our theory took the slightest interest in this *fact*, it would be realized that the ideal treatment of cancer should deliberately aim at the stroma, trying to sensitize it, make it more keenly aware of the presence of strangers. Moreover, it would have been noticed that this ideal line of treatment has been actually followed—though inadvertently—in radiotherapy.

I think it is time that those responsible for the treatment of our cancer patients should stop fooling themselves about what they are doing. A malignant tumour regresses after irradiation, not because the tumour cells are killed electively and the healthy cells left undamaged, but because a stroma reaction has been set up by irradiation, and it is this, indeed, which has a stupendous effect on the tumour. This is an elementary fact established beyond doubt. It has also been proved that the destruction of normal cells in the tumour bed is essential for the success of radiation. What makes a tumour "radio-sensitive" or "radio-resistant" is not the character of the tumour cells, but the amount and the character of the *stroma* and its reactive capacity.

Every radiotherapist knows that a "satisfactory" healing reaction is indispensable for the regression of a growth; he also knows that repeated small doses of irradiation (which maintain the healing reaction) are more effective than a single massive dose (which destroys the reactive tissues). Why does he not give up the frivolous notion of "tumour doses" lethal to the cancer cells and begin to think in terms of "stroma doses" necessary to enforce the right reaction? He can be sure of success in his practice every time he deliberately enforces a natural healing process; his results will be disappointing if he goes out to kill cancer cells.

The surgeon can greatly benefit from the experience of radiotherapy and the lesson drawn from it. When he reflects, like Dr. Riggall, upon the usefulness of those "ever-widening anatomical exercises done on the operating table" in search for cancer cells, it may occur to him that the theory of radical surgery cannot be sound. Once equipped with a biological theory which is in harmony with the facts of natural history, the cancer surgeon cannot fail to develop methods far superior to those of radiotherapy, methods designed to imitate and to improve upon Nature's healing processes.—I am, etc.,

London, N.8. F. M. LEHMANN.

Educating the Public about Cancer

SIR,—I have read with great interest your leading article on "Progress of Cancer" (May 24, p. 1119). In this you refer to the work of Swynnerton and Truelove, and also of Foulds, and I agree with your statement that "the application of these principles to the prognosis of 'early' and 'late' tumours is especially timely."

You also mention McKinnon, whose idea that early treatment and cancer education are useless is well known, but there is not one word in the reports of these workers to justify such an assumption. Swynnerton and Truelove (*British Medical Journal*, February 9, p. 287), when writing about the higher survival rate in those patients treated for gastric carcinoma after a long pre-operative history than in those with symptoms of shorter duration, go on to say, "This finding should not be taken to indicate that early diagnosis is of little consequence. On the contrary, we believe that every effort should be made to shorten the time between the onset of symptoms and the making of the diagnosis."

Turning now to Foulds's published lecture (*Ann. roy. Coll. Surg. Engl.*, 1951, **9**, 93), in which the author uses the word "progression" to indicate various irreversible changes that may occur in a tumour, and which may be grouped under the term malignancy, he says, "At its first clinical appearance a tumour may be at any stage of progression," and, further on, "Progression may be abrupt or gradual." The fact that in some growths progression is abrupt and advanced when the patient is first seen must not prevent every effort being made to diagnose those growths in which progression is gradual, and this can only be done by cancer education among the public. The question of how many lives can be saved by such methods can only be found out by a carefully planned research in a limited area.—I am, etc.,

London, W.14. MALCOLM DONALDSON.

Limitations of Chemotherapy in Tuberculosis

SIR,—A warm welcome must be given to the report (May 31, p. 1157) of the Medical Research Council on "Prevention of Streptomycin Resistance by Combined Therapy" and to the related article on "Chemotherapy of Pulmonary Tuberculosis in Young Adults." As you indicate in the generally admirable summary in your leading article, these investigations should serve as a model for such clinical trials, but the sentence, "With the publication of these reports the standard treatment for tuberculosis, at least in this form, may be said to be defined," may be misunderstood, and whether "form" refers to tuberculosis or to treatment may mislead the hasty reader.

The authors of these masterly reports, who state (p. 1167) that their findings relate to short-term results only, make no such claim. The reports deal with a particular variety of pulmonary tuberculosis in a selected age group treated by chemotherapy in a particular way, and at the end of six months of combined chemotherapy 75% were sputum-positive. Experience would lead one to fear that, without other forms of treatment, that proportion would rise with an extended period of observation. Often chemotherapy, even in the kind of tuberculosis dealt with in the reports, is but a means of bringing the patient to a stage, otherwise unattainable, when more radical treatment can be undertaken. Too often streptomycin is lavishly prescribed in forms of pulmonary tuberculosis in which it is ineffective, to the ultimate detriment of the patient who, left with a resistant strain of organism, may need it desperately at a later stage. It would be a pity if in the general acclamation, which these reports so richly merit, their scope and the limitations of present-day chemotherapy should go unheeded.—We are, etc.,

W. L. YELL.
N. A. NEVILLE.

Chelmsford.

Side-effects of Dihydrostreptomycin

SIR,—The report of Drs. Peter O. Leggat and John H. Gifford (May 10, p. 1008) on a woman with pulmonary tuberculosis exhibiting an uncommon side-effect of dihydrostreptomycin therapy prompts me to record a similar experience.

Two adult patients suffering from tuberculous meningitis required daily administration of cisternal streptomycin over a period of several weeks. Dihydrostreptomycin was used (before its harmful effect upon hearing was realized) in one case and streptomycin in the other. Prior to the use of the cisternal route, no diplopia or paralysis of the external ocular muscles was evident. Within a short time of each cisternal injection a coarse horizontal nystagmus and diplopia developed sufficient to interfere with the patients' pleasure in reading a book. These features persisted for the greater part of the day, and had nearly always disappeared before the cisternal puncture on the following morning. In one case, there occurred in addition a temporary weakness or complete paralysis of the lateral rectus muscle of the left eye a few hours after some cisternal streptomycin injections. This feature also persisted for the rest of the day, but had disappeared the following morning. When these two patients were able to revert to the lumbar route for intrathecal streptomycin the phenomena described no longer occurred.

It seems reasonable to ascribe these features to the intrathecal streptomycin, the cisternal route being in a position to affect the vestibular organs, the vestibular nerve, and even the vestibular nuclei in the brain stem to a greater extent than the lumbar route. There does not seem to be any explanation why the sixth cranial nerve should be involved in the case described here and the fourth nerve in the case described by Drs. Leggat and Gifford.—I am, etc.,

A. R. SOMNER.

Edinburgh.

Bone Marrow Depressed by Thiosemicarbazone

SIR,—We wish to report the occurrence of two cases of severe panhaemocytopenia in tuberculous women undergoing thiosemicarbazone therapy. In each case treatment was commenced with T.B.1 (*para*-acetylaminobenzaldehyde thiosemicarbazone), this being replaced by "ethizone" (*para*-ethylsulphonyl benzaldehyde thiosemicarbazone) when this preparation became available.

Case 1.—This woman was given T.B.1, 100 mg. daily for three months, from November, 1951, to February, 1952. On February 16 this was changed to ethizone, 100 mg. daily. She was well until May 5, when she developed bleeding of the gums. A week later she was admitted, with bleeding gums, purpura, and severe vaginal bleeding—haemoglobin 1.9 g. (13%), W.B.C.s 2,200 (24% neutrophils), platelets 58,000; bleeding time 15 minutes. Sternal marrow was at first qualitatively normal, but on May 19 was grossly hypoplastic.

Case 2.—This patient was given T.B.1, 100 mg. daily for six weeks, followed by 150 mg. daily for a further 18 weeks. In February, 1952, the drug was discontinued for a period of two months. On April 23 treatment was recommenced with ethizone, 150 mg. daily. Within 24 hours she had malaise, with fever and vomiting, but continued to take the drug. A week later she first noticed purpuric spots and that she was becoming pale. On May 20 she was admitted with extreme pallor and a purpuric rash —haemoglobin 2.8 g. (19%), W.B.C.s 2,300 (7% neutrophils), platelets 69,000. The sternal marrow was hyperplastic.

At the same time a considerable number of other cases in this district have been treated with thiosemicarbazones without serious ill effects. Cases of bone-marrow depression due to thiosemicarbazone therapy have been described before, particularly in the German literature. Therefore, we are not reporting a new condition. However, the reaction in our patients was unusually severe, and we feel that such cases should be brought to the attention of all doctors liable to prescribe this drug or to have the care of patients undergoing this form of treatment.—We are, etc.,

V. U. LUTWYCHE.
D. A. BREWERTON.

London, N.W.10.

Family Advice

SIR,—It is a commentary on the medical profession of our time that many patients avail themselves of the opportunities for extra medical advice offered by many magazines, including the successful *Family Doctor*.

The letters which come to a good-class magazine are of a surprisingly intelligent kind, and I would roughly classify their writers as follows: Those who do not wish to consult their doctor, or who frankly doubt his opinion (a small minority); those whose doctors are too busy or too unapproachable to explain the diagnosis or give details of the treatment they have ordered, such as diet; those who are too embarrassed to consult someone they know about intimate matters; and, lastly, those whose doctors are frankly uncooperative about the subject in question. In this last category comes the frequent request for information about facilities for preparation for "natural childbirth" during pregnancy, and for the names of sympathetic doctors, midwives, hospitals, and nursing-homes to which the reader can go for her confinement. There appear to be many intelligent young mothers who, having been made aware through reading or the testimonies of friends of the possibilities of a completely satisfying, conscious childbirth, are disheartened and thwarted in their efforts to find co-operation from our profession in achieving this.

I should welcome comments and suggestions for dealing with this sort of request. Just how many nursing-homes, hospitals, and public health authorities are interested in helping these enthusiastic young mothers, and is there any kind of register of them so that such people can be directed there if the private doctors prove unhelpful or even hostile?—I am, etc.,

GWYNETH M. COTTERELL.

Croydon.

Absence of Appendix

SIR,—With reference to the question and answer ("Any Questions?" May 26, 1951, p. 1215), and subsequent correspondence (July 14, 1951, p. 116, and September 15, 1951, p. 676), on absence of the appendix, I feel the following case may be of interest.

A negro woman aged 33 years consulted me for backache and attacks of abdominal pain. Two uterine fibroids were felt on examination and she was advised myomectomy. In accordance with my usual custom, on completing the myomectomy I proceeded to the removal of her appendix. The caecum appeared normal, but the terminal inch (2.5 cm.) or so of the ileum was adherent to the apex of the caecum. As the appendix was not immediately apparent, this part of the ileum was carefully dissected off, as I expected to find an appendix there. A thorough search (including palpation of the caecum) failed to reveal any trace of the appendix. The ileum was resutured back to the caecum and the incision closed. Recovery was uneventful.

This seems to me to be a definite case of complete congenital absence of the appendix.—I am, etc.,

Georgetown, British Guiana. N. N. IOVETZ-TERESHCHENKO.

Skin Rash at Cheltenham

SIR,—Your note on the recent epidemic skin rash at Cheltenham (*Journal*, May 31, p. 1203) quotes me as thinking it to be the same as that recorded by Schuppli from Basle in 1946 (not 1944).

Dr. G. B. Dowling drew my attention to Schuppli's report when the first Cheltenham cases appeared, and the resemblance is certainly close; but there is some doubt as to the complete similarity of the two epidemics. An exact cause has not been found for either, and therefore it would seem best at present to note that they are alike, without suggesting that they are identical.—I am, etc.,

Gloucester. ROBERT BOWERS.

Preventing Severe Surgical Shock with A.C.T.H.

SIR,—The medical memorandum by Mr. Alfred Beck (March 22, p. 636) was of considerable interest to us. For the past year we have been using A.C.T.H. before, during, and after surgery in selected cases. It seemed to us that there was good reason to believe that A.C.T.H. would often prevent or modify shock in long and severe operations. In the majority of cases in which the method has been employed we have felt convinced that shock has indeed been greatly lessened.

The technique has been to inject 10 to 20 mg. (units) A.C.T.H. (in an adult) some hours before operation and again after a lapse of four to six hours. Some patients have received further amounts on return to the ward. If the patient's condition permits, we think it wise to limit the A.C.T.H. to three or four doses, because there is some evidence that healing is delayed. Two of our patients had "burst abdomens," both having received A.C.T.H. for several days. This could be explained on other grounds possibly, but it has made us cautious.

We have applied the method in more than 40 cases now, and they have all been long and severe operations. Six "porta-caval shunts" (Mr. P. Theron), two pelvic exenterations (Mr. G. Charlewood), and several oesophagectomies are included.

As yet we have not used cortisone, but think it may be useful when a patient who is acutely ill has to undergo an operation. A.C.T.H. has been disappointing in some of these cases. This is perhaps to be expected, since the suprarenals probably have little reserve under these conditions.

It is our intention to submit a paper on this subject in the near future; but it is difficult to present it in a scientific manner because of the absence of controls. We are convinced of the efficacy of the method, and it does not seem justified to withhold it, if there is serious risk to life, in order to obtain controls.—We are, etc.,

D. C. DEVITT.
J. C. NICHOLSON.
K. B. VETTEN.

University of the Witwatersrand, Johannesburg.

Tragedy of Involutional Depression

SIR,—I wish to call attention to the lamentable state of affairs concerning the frequent lack of recognition of involutional depression, and the consequent denial of adequate treatment of this common psychiatric illness. In the last few years it has been my lot, in the course of my duties as a psychiatrist, to see scores of cases of this disorder, the majority of which, unfortunately, had been allowed to suffer untold misery for long periods before eventually they came within reach of specialist attention. This condition, as a rule, responds so dramatically to E.C.T. that in my view it is highly deplorable to deny this modern treatment to patients suffering from this distressing malady. Apart from the sufferings of the patient and the risk of suicide, the illness frequently entails considerable hardship to the patient's family, and in the aggregate no little loss of working capacity to the nation as a whole. Patients suffering from this complaint are often labelled as psychoneurotics or plain hypochondriacs, or quite often they are made to go through the whole gamut of costly and elaborate investigations before finally, after a long delay, they are referred to the psychiatrist. If all patients of the age group in question suffering from depression of some weeks' duration were promptly referred for opinion to the psychiatric physician a great deal of avoidable misery would be averted.—I am, etc.,

Cheddleton, near Leek, Staffs. CHARLES BORG.

Arterial Occlusion During Fit

SIR,—I was interested to read Dr. W. L. B. Leese's medical memorandum (April 19, p. 854) on the case of spontaneous arterial occlusion during an epileptic fit. A few weeks ago I saw in consultation a very similar case, the only difference being that this was induced by insulin.

A woman aged 48 was given insulin shock treatment for depression. Full limb oscillometric study had previously shown a normal peripheral vascular tree. In the latter stages of treatment she complained of pain on exertion in her right leg. A few days later she was suddenly seized with violent pain in her right leg, and examination showed complete occlusion of the right iliac, femoral, and profunda arteries. A subsequent arteriectomy confirmed this. With lumbar sympathectomy the circulation improved, and at present it seems as if the patient will lose only the terminal phalanges of the foot.

As there is no evidence of peripheral arterial disease elsewhere, one wonders how much damage to the intima of an artery can be caused by such therapy. Obviously this is a matter which requires fuller investigation.—I am, etc.,

London, W.1. E. M. HERBERT.

Pulmonary Embolism

SIR,—May I beg the hospitality of your columns to challenge Mr. McNeill Love's statement (April 26, p. 920) that any surgeon who fails to balance his patients' heels on a pillow is morally responsible for subsequent pulmonary embolism? There is no evidence that this manœuvre has any effect on the incidence of thrombo-embolic disease, nor that unconscious recumbency for an hour or so is a factor in its pathogenesis. This is indeed fortunate, as otherwise sunbathers, and people who make a habit of going to bed at night, would be in constant mortal peril. It is difficult to believe that such mild pressure could cause thrombosis in the well-cushioned muscle veins whilst leaving the superficial veins unscathed. It is even more difficult to ignore the much greater pressure on the buttocks.—I am, etc.,

Barnet, Herts. V. J. DOWNIE.

Discharge of Certified Mental Patients

SIR,—It is a pity that the amended Section 72 of the Lunacy Act, 1890, should have received such undeservedly harsh criticism (May 31, p. 1193). It is possible that conditions vary from area to area, but in my experience relatives of patients are by no means as unreasonable as alleged, and they rarely abuse the new freedom given them. With very few exceptions they accept the advice of the hospital specialist. In the difficult case I have been able to persuade the appropriate relative to take the patient out on trial (Section 55), and this will demonstrate that the patient is not fit to be out; the added weight of the family doctor's opinion will help here, as Dr. C. A. Watts points out (May 31, p. 1193).

The law can indeed be made to appear farcical, as Dr. A. Walk demonstrates (May 31, p. 1193), but the pertinent question is, How often do the types of cases quoted occur among the many thousands being discharged? I submit that such cases constitute only a very small proportion of the total. The occasional difficulty created is more than counter-balanced by the many advantages of the amended Section 72, one of the most important of which is the knowledge by the public that it is easy to arrange for the discharge of the great majority of certified patients, be they recovered or not. Not that such knowledge must necessarily pass into immediate action. There have been no wholesale discharges ordered and mental hospitals are as overcrowded as ever. As a rule relatives do not wish to have at home patients who are a disturbing nuisance, in fact they generally expect such patients not only to be well behaved but to be also capable of gainful employment. The essence of freedom is a psychological one—the knowledge that one is not debarred from a particular type of action if one should ever desire it. The idea that once a person is certified he is of a necessity incarcerated permanently has lingered for so long that it is high time the Law introduced a measure to eradicate such an undesirable belief. The new freedom has destroyed the notion that committees and superintendents must be permanent jailers of any patient, unless indeed such a person is positively dangerous. And here permit me to comment on the interpretation of Section 74. I have tried to obtain from a high source, without success, a precise legal definition of the phrase, "Dangerous and unfit to be at large." I doubt whether Dr. O. FitzGerald's wide interpretations (May 17, p. 1082) could be upheld in a Court of Law, and I would not like to see this happen, as there is a danger that Section 74 might be interpreted in such an excessively ingenious manner as to render the freedom of Section 72 farcical. The phrase, "Dangerous and unfit," should signify evidence of homicidal or suicidal propensities, or of some such serious behaviour disturbance as pyromania.

—I am, etc.,

Basingstoke. I. ATKIN.

In Memory of Dr. Montessori

SIR,—All those who work seriously in "the new pedagogics" initiated by Dr. Montessori realize that public appreciation of this fails almost inevitably to grasp the true basis of its claim to scientific status. All the more pleasing it would be if the medical world were willing to do so.

History seems to confirm that both Pestalozzi and Tolstoy stumbled, as it were, accidentally on the phenomenon of spontaneous work in childhood, but they lost sight of it again and failed to recapture it. Montessori, like them, saw it unexpectedly, but—unlike them—succeeded in capturing it by studying the conditions favourable to its appearance. This is a most unusual, yet wholly objective, form of research, for unfavourable conditions are immediately indicated by its disappearance. Biology knows the dependence of every living being upon its environment, but it is a new thing to trace connexions between this and the higher mental characters of man.

Montessori succeeded so well in fitting the environment to the child (and this includes the behaviour towards him of his attendant adult) that she was able to bring within the orbit of his spontaneous activity the assimilation of all aspects of the culture into which he was born (history, geography, languages, algebra, etc., included). The teacher's three functions of guardian, teacher, and observer, which seem antithetical, can be blended artistically to make an almost strainless child-adult relationship, and the increased well-being and happiness to both sides seem to indicate a path to mental health which could well prove no less important than the path to physical health, known as hygiene.

—I am, etc.,

Montessori Training College, Cranleigh, Surrey. CLAUDE A. CLAREMONT, Principal.

Emergency Bed Service

SIR,—Please find space in your columns to publish these words of appreciation of the work done by the Emergency Bed Service in the London area. Little is published, all is accepted, of the help this organization gives to the general practitioner. Recently I received an invitation from our local division of the E.B.S. to take the opportunity of calling on them during the day and seeing the Service at work. This I was delighted to accept, but was amazed to be informed by the Secretary that no less than one dozen general practitioners had called during the hours of 10 a.m. and 6 p.m.

I saw this very efficient and courteous organization at work, and now fully appreciate when the working practitioner is over-anxious to have his patient admitted to hospital, whether for investigation or immediate surgical treatment, how important it is for him to give every possible clinical sign he can detect to make the work of this very fine Service less arduous.—I am, etc.,

London, E.10. D. P. FITZGERALD.

POINTS FROM LETTERS

Latin Comes to Life

Dr. G. G. SHERRIFF (London, W.8) writes: I suggest with respect that the preferable plural of meatus is meatus, rather than meatuses. Indeed, this is the first choice of the *Concise Oxford Dictionary*.

Dr. V. L. FERGUSON (Nottingham) writes: In Points from Letters (May 31, p. 1197) your apologies to Mr. Watson Williams strike me as incredibly funny. You say that in your effort to keep Latin alive you use the word "meati" whereas it should have been "meatuses." It should be neither the one nor the other. All this reminds me of a story I heard recently of two business men meeting. One said to the other, "Isn't business lousy?" and the reply was, "Do not speak disrespectfully of the dead." Now that editorial Latin is dying your readers will be anxious not to speak disrespectfully of it.

["*Esto peccator et pecca fortiter . . .*" Following this doubtful precept, we erred in the footnote on p. 1197 of the *Journal* of May 31: *peccavimus*, for those who like it this way. As meatus has been in English usage for nearly 300 years it is time it had an English plural, and "meatuses" is sanctioned by the *O.E.D.* Every fourth-form schoolboy knows that meatūs is a fourth-declension noun and that its plural is meatūs. Drs. Ferguson and Sherriff are both right and wrong—right in detecting a shocking editorial lapse and wrong, we think, in their preference. On this question of Latin plurals Fowler wisely remarks: "All that can safely be said is that there is a tendency to abandon the Latin plurals. . . ." So from henceforth let it be "meatuses." —ED., *B.M.J.*]

The Progress of Cancer

Mr. J. COLE (University Laboratory of Physiology, Oxford) writes: Your leading article (May 24, p. 1119) concludes by referring to the "urgently needed study of the behaviour of untreated cancer in man." An early study on this subject is to be found in *Mr. William Lilly's History of His Life and Times from the year 1602 to 1681* (Lond. 1715). In this account Lilly, the astrologer, at that time a 20-year-old apprentice to Gilbert Wright, of London, describes the illness and death at the age of 70 of his Master's wife in the following terms:

"*Of my Mistress's Death, and Occasion thereof by Means of a Cancer in her Breast.*—In 1622 she complained of a Pain in her left Breast whereon there appeared at first a hard knob no bigger than a small Peason; it increased in a little time very much, was very hard, and sometimes would look very Red; she took advice of Surgeons, had Oils, Sear Cloths, Plates of Lead, and what not: In 1623 it grew very big and spread all over her breast; then for many Weeks Pultises were apply'd to it, which in continuance of time broke the Skin, and then abundance of watery thin Stuff came from it, but nothing else; at length the Matter came to Suppuration, but never any great store issued forth; it was exceeding noisome and painful; from the beginning of it until she died, she would permit no Surgeon to dress it but only myself; I applied everything unto it, and her Pains were so great the Winter before she died, that I have been called out of my Bed two or three Times in one Night to dress it and change Plaisters. In 1624 by degrees with Sizzers I cut all the whole Breast away, I mean the Sinews, Nerves, etc.

"In one Fortnight, or little more, it appeared, as it were, mere Flesh, all raw, so that she could scarce endure any Unguent to be applied.

"I remember there was a great Cleft through the Middle of the Breast which when that fully appeared she died which was in September 1624."

Obituary

Dr. WILLIAM JOHN FORBES, who was in practice for many years at Knaresborough, Yorkshire, died at his home there on April 22, aged 81. Born on May 9, 1870, he was educated at Queen's (now University) College, Galway, and at Queen's College (now University), Belfast, graduating M.B., B.Ch. from the old Royal University of Ireland in 1893. After a year in private practice in Ireland, he came to England as an assistant in a practice at Sutton-in-Ashfield, Nottinghamshire, moving to Knaresborough in 1896 and remaining in active work there until the time of his death. Dr. Forbes became surgeon to the Knaresborough Dispensary and for many years he was the part-time medical officer of health to the rural district council. He was also the factory doctor for the area, and Treasury medical officer. A member of the British Medical Association for 58 years, Dr. Forbes was chairman of the Harrogate Division in 1938–9. He leaves a widow, to whom we extend our deepest sympathy.

Dr. E. GARNEYS WALES, who died on May 3, at the age of 75, was the fourth generation of a family of doctors, all trained at Guy's Hospital, who practised from the same house in Downham Market in Norfolk. Thomas Wales, a native of Walberswick, Suffolk, founded the practice in 1792. He was a grandson, on his mother's side, of John Copland, physician to George III, whose gold-headed cane he inherited. Another heirloom that Thomas left was a Royal Humane Society medal which was presented to him in 1803 on the occasion of his saving a Mr. Thomas Farrow from drowning. This must have been one of the earliest occasions on which this medal was awarded. In 1816 Thomas Wales was joined in the practice by his son, Thomas Garneys Wales, who continued to practise for 49 years and achieved a great reputation as a midwife. He appears to have been a man of few vices, apart from the smoking of strong tobacco, and many virtues, as may be judged from letters of appreciation written on his death in 1870 by Sir James Paget, Sir George Humphrey, Sir George Paget, and others. Of his 12 children, only five survived to adult life, the other seven all dying of whooping-cough. In 1855 he was joined in the practice by his son, Thomas Garneys Wales, junior, the father of Edward Garneys Wales, who was born in 1832, five years before Queen Victoria's accession. He was a typical Victorian, top-hatted and bearded. Kindly and quiet, with a strong sense of humour, he was devoted to his profession and to his family, and was deservedly loved by his patients. In 1917 he retired at the age of 83, though in the following year he returned to practise for a short time during the great influenza epidemic, being the only doctor in the neighbourhood to escape the infection.

For the following appreciation of Dr. E. Garneys Wales we are indebted to Dr. G. M. S. Leedham-Green: Edward Garneys Wales was educated at Charterhouse, Downing College (to which he won a scholarship), and Guy's Hospital. He qualified M.R.C.S., L.R.C.P. in 1901, and took the degrees of M.B., B.Chir. in the following year. He then returned home to join his father in the family practice, and became "the young doctor," a title he retained until his father died a quarter of a century later at the age of 93. It was a hard life to which he returned, but an enjoyable one, except for the incessant night work. He attended about 100 maternity cases a year, and the only help was from incompetent, usually dirty, old gamps who were responsible for many useless night journeys, many false alarms, and much tedious waiting. Nearly all these cases were at a guinea apiece, and he thought himself lucky if he got it. The state of the fen roads at that time was appalling, especially in the winter, and for nearly 14 years Dr. Wales did the bulk of his visits on horseback, with a lot of cycling in the summer. With his inherited sense of service and a knowledge of his patients and their forefathers extending by oral tradition for over a hundred years, he was more than a good physician. To all his patients he was a personal friend, whose counsel extended far beyond the consulting-room. This tradition of long and faithful service was evidently infectious. Three coachmen in the service of the Wales family covered between them a total of 105 years. The old dispenser, who died this year, over 80 years of age, came to the firm when he was 21 and reported daily to within a few weeks of his death. It was to him that Edward Wales remarked in connexion with an old bottle labelled "Tinct. Humuli" and formerly the property of the first Thomas Wales: "Has this bottle ever been used?" The considered reply was, "Not in recent years, sir." Tincture of Mould may now be out of date, but its refined descendants stand on the same shelves today. Dr. Wales was an artist of considerable merit, and when ill-health forced him to give up practice in 1937 he went (with an artist's appreciation of rounding off the circle) to live at Southwold, within sight of the place which old Thomas Wales left in 1790. He remained gay and cheerful in his retirement, delighting in the company of old friends and new, and dispensing a warm hospitality. His first wife died soon after he had retired. The sympathy of all his friends goes to his widow, his second beloved wife, to whose skill and loving care he owed so much.

We record with regret the death of Dr. JOHN PENMAN at his home at Birkdale, Lancashire, on May 11. He graduated M.B., Ch.B. from the University of Glasgow in 1910, and, after a house appointment at Southport Infirmary and an assistantship in Manchester, he settled at Colne, Lancashire, where for many years he conducted a large practice and was on the visiting staff of the Hartley Hospital. During the war of 1914–18 he served overseas with the R.A.M.C. Persuaded to seek some prospect of leisure, he moved from Colne to semi-retirement at Southport in 1935, but he was soon as fully occupied as before. From his earliest student days his resolute aim was sound general practice in the highest traditions of the family doctor, and to this ideal he steadfastly devoted his life with a constancy and a fidelity that won for him that which he treasured most, the respect and affection of innumerable friends. Now, after 42 years' service in the work he loved, his loss is mourned by colleagues and patients alike. He was a kindly, lovable man and an amiable host. He is survived by his widow and two daughters.—J. I. R.

Medico-Legal

AMERICAN LEGACY TO NATIONALIZED HOSPITALS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Mr. E. Stanley Holland was born near Leominster in Herefordshire. At a mature age he crossed the Atlantic, settled in Chicago, became a naturalized citizen of the United States, and amassed a considerable fortune as a contractor. He died unmarried in Chicago in 1936, leaving certain brothers, sisters, nephews, and nieces surviving him in England.

During his life he often visited England and made liberal gifts to various Herefordshire charities. He was a life governor of Leominster Cottage Hospital, to which he made substantial contributions during his lifetime, including the construction of a women's ward and the equipment of an *x*-ray department.

By his will he left the residue of his estate, after providing for various specific bequests, in trust for various members of his family for their lives. On their deaths part of the residue was to be administered for the benefit of certain of

his relations, and the rest was to be distributed in stated proportions among King Edward's Hospital Fund for London and three named hospitals—the Hereford General Hospital, Leominster Cottage Hospital, and the Hereford Eye and Ear Hospital. These beneficiaries were to use their shares as endowment funds, only the income being used for current expenditure.

Recently the trustees of Mr. Holland's will issued a summons in the Illinois Court in Chancery asking the Court for directions as to the disposition of the residue, having regard to the effect on the King Edward's Hospital Fund and the three hospitals of the National Health Service Act in England.

The court found no difficulty in deciding that King Edward's Hospital Fund was still in existence as a separate corporation and was essentially unaffected by the Act.

As to the bequest to the hospitals, Mr. Holland's relatives contended that the gifts were specific and failed as a result of the nationalization of the hospitals under the Act; that the *cy près* doctrine, by which on the failure of a specific charitable bequest if the testator made it with a general charitable intention the court can order the property to be used for a similar purpose, did not apply under the law of Illinois which controlled the matter; and that accordingly there was a resulting trust in favour of the testator's heirs.

The hospitals were represented by H.M. Attorney-General, who contended that the gifts were made with a general charitable intention and therefore did not fail; that, if they had failed, the *cy près* doctrine applied under the law of Illinois; and that in any event they amounted to vested equitable remainders and that their disposition was by the law of Illinois to be made according to English law, including the provisions of the National Health Service Act, so that the trustees were bound to apply them for the benefit of the appropriate regional hospital board or hospital management committee.

Judge Samuel B. Epstein came to the conclusion that the will showed unmistakably that the gifts were made with a general charitable intent. He was prepared to hold that, apart from the *cy près* doctrine, he would be justified in designating the Birmingham Regional Hospital Board or the Herefordshire Hospital Management Committee as the organizations to administer the gifts, especially as the Attorney-General had expressed the willingness of the English Government to undertake that the funds would be held and disposed of for the benefit of the designated hospitals and no others, as provided by the will.

Judge Epstein also held that *cy près* doctrine did apply in the law of Illinois, and said that it was hard to imagine a case more appropriate for its application, since the nationalized hospitals were the identical institutions designated by the testator, rendering the same type of medical service to the same community, in the very same buildings and using the very same facilities. He also held that the bequest gave the hospitals a vested remainder, with only the enjoyment postponed. While Illinois law controlled the interpretation of the will creating the trust in which the trustee and the trust residue were located in Illinois, the disposition of the vested interests under such a will was governed by the laws of the domicile of the donor, and therefore the provisions of s. 60 of the National Health Service Act applied.

As the judge said, the wisdom or lack of wisdom of the adoption by the English Parliament of the National Health Service Act was no concern of the court, nor was it endorsing by its decision the system known as "Social Medicine." The regimentation of the medical professions in England might well be detrimental to medical service. It was certainly contrary to the American conception of free enterprise. The nationalization of hospitals did not, however, detract from the worthiness of any charitable bequest for their support.

Universities and Colleges

UNIVERSITY OF OXFORD

Mrs. Antoinette Pirie, M.A., Margaret Ogilvie's Reader in Ophthalmology, has been elected to a Professorial Fellowship at Somerville College.

UNIVERSITY OF CAMBRIDGE

On June 3 Sir Lionel Whitby, Master of Downing College and Regius Professor of Physic, was re-elected Vice-Chancellor of the University for 1952–3.

In Congregation on June 5 the honorary degree of Sc.D. was conferred on Surgeon Rear-Admiral Sir Gordon Gordon-Taylor, Consulting Surgeon to the Royal Navy and to the Middlesex Hospital.

UNIVERSITY OF LONDON

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 6]R. L. B. Beare, [1 7]O. Dansie, [1 4]H. T. Davies, [1 7]J. A. Fleming, [1 7]Grace E. S. Forrest, [1 3]E. D. Fox, [1 2]E. J. G. Glencross, [1 4 6]A. Guz, [1 7]R. F. Jackson, [1 4]Daphne M. Kirkman, [1 7]B. L. Mallett, [1 4]P. O. P. Newell, [1 3]P. M. Phillips, [1 3 4 7]G. Sandler (*University Medal*), [1 4]Gillian E. M. Tarnoky, [1 6]D. W. Vere, [1 3 4]W. D. White, [1 3]D. C. Wilkins, Pauline A. Adams, R. K. Allday, G. A. Ames, A. G. Amias, D. A. Andrews, J. R. Andrews, T. C. R. Archer, B. K. Arthur, J. R. Aston, K. D. Bagshawe, R. C. Baillie, Elizabeth M. R. Bakirgian, G. T. Balean, G. V. Balmforth, P. J. Barclay, S. S. Barker, D. T. C. Barlow, Mildred M. E. Barnard, Rosalind A. Barnes, J. W. B. Barnett, P. K. M. Barrett, W. G. Barry, F. J. Bateman, D. N. Bates, D. H. Bayton, H. S. Bedson, C. L. Belcourt, J. S. Beresford, Hilary A. Berry, Phyllis E. Billinge, E. W. G. Birch, G. W. Bisset, A. S. Blake, W. R. Blatchley, J. N. Blau, D. G. Bluett, H. M. J. Bogaerts, R. F. Bolam, J. P. Bomford, Gisela Boss, B. C. W. Boyd, E. A. Boyse, D. W. Bray, L. H. Brearley, J. Brittain, R. W. Brotherwood, F. P. Brown, G. L. Brown, Helen E. Brown, J. D. Bruce, C. J. Buckingham, I. H. Buckland, C. V. Bullen, H. A. Burgess, Winifred Burgess, A. M. Burnford, T. K. H. Burnham, J. D. K. Burton, Alison M. Bush, D. G. Calvert, H. J. Carne, D. M. Carter, Stephanie J. Carter, J. D. H. Cave, J. Cherry, E. E. Clapham, Sylvia J. Clapp, J. A. Clappen, Barbara C. Clark, H. L. Clarke, R. J. S. Clarke, Heather R. Clay, R. C. Cochrane, M. Cohen, F. J. J. Coleman, C. M. Conway, Josephine Cook, T. S. Cookson, P. B. Counsell, Barbara M. St. J. Coventry, Mary Crawford, Etain A. Cronin, L. Crouch, D. Ll. Crowther, Daphne I. L. Da Costa, T. A. Daff, Melfyn Davies, M. L. Davis, B. H. Day, J. R. Deacon, L. C. Dean, A. J. H. de Kretser, J. Dennis, M. F. Dixon, J. S. Dodge, Josephine Dolan, W. A. C. Dow, Marie G. Drew, H. T. Duke, J. Eastwood, P. S. Elias, R. S. K. Essame, A. J. Evans, R. R. Evans, N. H. Eve, E. J. Fairlie, J. P. Farrell, I. R. Ferdinand, Elizabeth Fincham, P. Fincham, R. F. Fisher, B. Fistein, W. P. Fitt, Freda Fleischer, D. J. Flight, R. J. Flight, H. T. Ford, A. D. Fox, R. E. Frears, P. Freilich, Eva A. Frommer, N. P. H. Gibbs, C. H. Gill, J. A. Girling, L. P. Goodchild, A. H. Goodspeed, J. A. Gorst, Hilary B. Gostling, K. L. Granville-Grossman, Elizabeth I. Greenlaw, D. F. Hadman, I. G. Hamilton, D. O. Hancock, R. L. Hardway, D. C. Harris, J. Harrop, J. Hart, J. D. Harte, Charlotte Hartstein, R. B. Hawes, E. G. Haydon, J. H. Heard, F. L. P. Heber, J. Heckford, P. A. Henderson, Josephine C. M. Heylen, B. K. Higgins, Pamela E. Higgins, J. H. Highman, N. A. Hiley, J. MacL. Hill, R. F. Hindley-Smith, Dinah J. Hony, W. D. Hopkins, D. J. Hosking, N. F. W. Howorth, J. P. Hughes, F. C. Hurrell, B. Hynes, G. H. Isaac, B. G. Jackson, D. A. T. Jackson, A. Jacobs, E. R. Johns, Isabel D. Johnson, A. O. Jones, Marie H. Kallberg, P. E. Kapff, Joan Kelly, P. J. King, Sylvia L. Kingsbury, R. M. Kirk, E. T. Knudsen, D. B. Laird, B. D. Lascelles, Barbara Lawrence, Phyllis G. Lemon, E. Lewis, C. A. Linsell, H. I. Lockett, L. D. Lord, K. R. Lown, Margaret Luing, D. J. McBrien, N. B. McDiarmid, D. A. F. McGill, S. N. Maclennan, I. Macmillan, Pamela M. McMorran, D. McQueen, D. J. Manton, G. A. Marin, J. W. Markham, I. G. Marsh, C. R. A. Martin, W. A. Matheson, Joan M. Mawer, D. C. Mayr, P. D. Meers, Geeta S. Mehta, Morag J. R. Millar, H. A. Milne, C. A. C. Mims, D. N. Mitchell, H. Montgomery, K. S. Mooleedhar, J. D. Moore, C. W. Morley, Rosemary A. Morrell, Eleanor Morrison, K. E. Mortimer, D. A. J. Neden, W. T. Newman, Joan M. Newton, R. G. Newton, R. G. Nichols, Elizabeth M. Nicholson, Jean J. S. Nicolson, Margaret A.

Norman, Joyce B. Nunneley, R. M. Oliver, C. H. Opie, J. A. Page, N. S. Painter, C. A. L. Palmer, R. A. Pargiter, J. C. Parkes, P. M. Pawsey, Mary C. Peard, Millicent J. Pentney, K. C. Perry, L. J. Phillips, H. B. Polak, N. T. Pollitt, K. R. S. Pool, G. H. G. Poole, M. E. A. Powell, Felicity Prestige, G. C. Pretty, E. C. V. Price, J. H. Price, M. G. Price, Freda E. Prince-White, F. N. Prior, D. A. Rands, Anne M. Ranken, Valery Rayner, R. A. S. Redd, V. J. Redding, G. D. Rees, H. S. Reeve, G. H. Renton, J. M. Ritchie, D. S. Robinson, R. B. Robinson, J. A. Rogers, Eleanor T. Rolston, B. H. Ross, H. B. Ross, Patricia A. Russell, Ursula M. Ruston, H. Salmon, W. M. Sare, D. M. M. Sayers, Margaret Schafran, R. J. Schen, J. E. Scriven, W. Sewell, F. C. Shelley, P. M. Shore, H. L. Silver, I. H. S. Silver, G. B. Skinner, A. C. R. Skynner, J. G. Slater, G. I. Small, A. J. Smith, B. A. Smith, D. C. Smith, R. C. Smith, J. D. Somper, A. Spellman, E. C. Spencer, G. W. Sprigge, R. M. Stanford, Mary J. Starbuck, A. E. Stevens, J. C. J. Stoke, A. E. Strigner, G. A. Stroud, Mary W. Sturges, G. H. Sullivan, M. W. Swallow, Mary T. Taylor, G. G. Thomas, G. E. M. Thomas, J. D. Thomas, R. E. M. Thompson, H. H. Thomson, B. J. Todd, J. N. Todd, Molly E. Towell, P. Train, P. E. Tucker, M. E. Tunstall, Annemarie D. Tupper, Prudence Valentine, G. W. Waddy, P. O. Wakelin, Phyllis M. Wallington, R. W. Wallis, Joanna M. Ward, C. H. W. Warne, L. P. E. Watson, M. B. Watts, R. S. Wells, G. F. Westcott, H. R. Whitaker, Ingeborg R. Wiernik, L. Williams, M. C. Williams, J. H. Willis, H. J. W. Willson, J. M. Wilson, V. Wilson, J. K. Wing, F. Winston, P. A. Woodbridge, Susannah M. Woodcock, W. A. A. Woodruff, C. I. Woolf, Dorothy E. Wright, P. A. C. Wright, J. K. N. Yearsley, A. C. Young, H. L. Young, A. Zisserman, P. A. Zorab.

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in hygiene and forensic medicine. [4]Distinguished in medicine. [5]Distinguished in applied pharmacology and therapeutics. [6]Distinguished in surgery. [7]Distinguished in obstetrics and gynaecology.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL

The object of the Wiltshire Memorial Research Scholarship is to encourage research in cardiology in its widest aspect. It is tenable for one year, but may be renewed, and it may be held for the purpose of study and travel abroad. The holder must be a registered medical practitioner, and the appointment, which may be part-time or full-time, carries with it an honorarium of at least £400 a year. Inquiries concerning the scholarship, which is now available for award, should be addressed to the Dean, King's College Hospital Medical School, Denmark Hill, London, S.E.5.

UNIVERSITY OF MANCHESTER

Horace Gray Radden, D.D.Sc., F.D.S. R.C.S., at present professor of dental science in the University of Western Australia and director of the Perth Dental Hospital, has been appointed professor of dental surgery in the University of Manchester, in succession to Professor F. C. Wilkinson, M.D., D.D.Sc., F.D.S. R.C.S.

QUEEN'S UNIVERSITY, BELFAST

Graham MacGregor Bull, M.D., M.R.C.P., has been appointed Professor of Medicine, in place of the late Sir William Thomson, and John Joseph Pritchard, D.M., Professor of Anatomy, in the place of the late Professor Thomas Walmsley.

Professor Bull was born in South Africa, of Scottish parentage, and was educated at the University of Capetown, where he graduated M.B., Ch.B. in 1939, proceeding M.D. in 1947. He was elected M.R.C.P. in 1947, in which year he came to London on a research fellowship to the British Postgraduate Medical School. Since 1948 he has been physician to Hammersmith Hospital and lecturer in medicine at the school. In future the chair of medicine at Queen's University is to be a full-time one.

Professor Pritchard is a native of Adelaide, South Australia, and was educated at St. Peter's College and at the University of Adelaide, where he graduated B.Sc. in 1934. In the following year he came to England as a Rhodes scholar at Magdalen College, Oxford. He received his medical training at St. Bartholomew's Hospital, graduating B.M., B.Ch. in 1941. He proceeded D.M. this year. From 1941 to 1949 he was assistant lecturer at St. Mary's Hospital, London, then senior lecturer, and finally reader in human anatomy. Since 1948 he has been a member of the board of studies in human anatomy at the University of London.

Dr. R. F. Whelan has been appointed to a lectureship in physiology, with special responsibility for dental students, and Dr. John Simpson to a temporary lectureship in preventive medicine in the university.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College held on May 21, with Professor Walter Mercer, President, in the chair, the following candidates, who had passed the requisite examinations, were admitted Fellows: S. Abul-Husn, D. H. Biggs, C. B. Cornish, R. P. Cumming, B. M. de Saxe, Amy D. Engineer, W. Grundill, R. Habib-Ur, J. D. Hennessy, J. S. Karanwal, A. Marshall, J. M. Mehta, A. H. Moore, H. D. Rawson, T. F. Redman, A. E. Rublack, D. P. Short, G. A. Silley, L. Simon, P. R. Toddywala, D. M. Whitley.

SOCIETY OF APOTHECARIES OF LONDON

The following candidates have been approved at the examinations indicated:

L.M.S.S.A.—A. Levisohn, R. E. H. Jones, F. D'U. Burgess, G. E. Sharp, E. J. Stacey, J. A. Marais, H. C. Cunningham, T. J. Stanton, A. H. Barker, K. G. Somers-De Haney, G. M. Gaskell, N. P. Burns, H. St. J. Mansbridge, M. C. Shah, W. R. Shanks, R. D. France, M. Kassab, J. W. Leach, D. M. Carter, R. C. H. Ladell, I. A. Campbell, R. E. Fryer, A. G. Hilmy, J. P. Turner, P. J. H. Cheong, L. J. Miller, J. H. Kerr, C. M. Stafford, P. W. Weston, C. P. B. Brook, V. S. Nicholson, P. G. Woolf, G. F. Lambert-Porter, P. F. Knight, L. A. Lees.

M.M.S.A.—M. I. Cookson, G. E. Peters, S. E. Sash, E. N. S. D'Arcy.

DIPLOMA IN INDUSTRIAL HEALTH.—W. F. Felton, D. G. R. Fox.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College, held on May 24, with the President, Dame Hilda Lloyd, in the chair, the following were elected to the Council to fill statutory and other vacancies: *As representatives of the Fellows*, O'D. T. D. Browne, G. F. Gibberd, H. J. Malkin, S. W. Maslen-Jones; *as representatives of the Members*, G. Boyd, L. B. Patrick.

The following were admitted to the Fellowship: Y. N. Ajinkya, A. W. Andison, A. Josephine M. T. Barnes, C. W. F. Burnett, W. D. A. Callam, G. P. Charlewood, S. Davidson, R. de Soldenhoff, A. B. Evans, D. B. Fraser, H. F. P. Grafton, N. McA. Gregg, G. G. Lennon, W. A. Liston, R. Lyons, H. McLaren, R. F. Matters, B. E. Meek, H. K. Porter, P. G. Preston, D. C. Racker, G. W. Robson, J. W. Schabort, G. G. L. Stening, S. L. Townsend, J. C. Whyte, R. J. Wotherspoon.

The following were admitted to the Membership: E. McL. Barbour, Caroline D. Baugh, R. M. C. G. Beard, D. C. G. Bracken, K. McL. Crocker, V. Drosso, M. P. Durham, J. Elstub, B. Eton, M. R. Fell, H. Ferguson, C. M. Flood, F. G. Geldenhuys, V. B. Gokhale, P. F. C. Jackson, A. I. I. Klopper, J. B. Lawson, Sarah Lehane, A. D. McIntosh, D. Magner, D. Meagher, A. P. B. Mitchell, N. Moss, T. R. Nelson, Margaret B. Noble, C. B. Oxner, J. Price, H. I. Schmilg, W. H. D. Scotland, R. S. L. Stafford, Joan E. Storey, E. Sussman, J. S. Tomkinson, F. L. A. Vernon, J. Ward, P. P. Wium.

The Services

Major-General F. K. Escritt, O.B.E., late R.A.M.C., has been appointed Honorary Surgeon to the Queen in succession to Lieutenant-General Sir Neil Cantlie, K.B.E., C.B., M.C., late R.A.M.C., retired.

Lieutenant-Colonel D. N. Nicholson, T.D., has been appointed Surgeon on the staff of Officers of The Queen's Body Guard for Scotland, Royal Company of Archers, in succession to the late Lieutenant-Colonel J. R. C. Greenlees, D.S.O. (Bar).

Major (Honorary Lieutenant-Colonel) W. O'Callaghan and Captain (Honorary Major) W. N. Chisholm, M.B.E., R.A.M.C., have been awarded the Territorial Efficiency Decoration.

Major S. O. Bramwell, R.A.M.C., has been appointed M.B.E. (Military Division) in recognition of non-operational services in Japan in connexion with operations in Korea.

Major (Temporary) W. G. Miln, R.A.M.C., has been appointed M.B.E. (Military Division) and Lieutenant-Colonel A. Maclennan, O.B.E., and Captain P. M. Bretland, R.A.M.C., have been mentioned in dispatches in recognition of gallant and distinguished services in Korea during the period July 1 to December 31, 1951.

Professor B. W. Windeyer, M.B., F.R.C.S., D.M.R.E., F.F.R., Director of the Meyerstein Institute of Radiotherapy, Middlesex Hospital, London, W., has been appointed Honorary Consultant in Radiotherapy to the Royal Air Force.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending May 24 (No. 21) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	25	3	7	0		43	3	13	2	2
Dysentery	269	38	69	10	2	689	153	129	1	1
Encephalitis, acute	2	0	1	0		2	0	0	0	
Enteric fever:										
Typhoid	1	0	0	0		5	0	1	3	0
Paratyphoid	53	0	6(B)	1	1(B)	15	1	1(B)	0	
Food-poisoning	127	20		0		96	13		2	
Infective enteritis or diarrhoea under 2 years				5	32				17	18
Measles*	6,242	330	413	247	478	19,189	748	424	263	263
Meningococcal infection	42	5	21	1	2	41	2	18	0	1
Ophthalmia neonatorum	44	7	8	0		28	0	14	0	
Pneumonia†	429	22	193	6		613	34	188	7	1
Poliomyelitis, acute:										
Paralytic	18	1	2	1	2	22	1	4	0	2
Non-paralytic	19	3				8	2			
Puerperal fever§	254	39	14	0		99	11	11	1	2
Scarlet fever	970	70	174	14	50	933	66	164	22	62
Tuberculosis:										
Respiratory			174	34				207	51	
Non-respiratory			42	11				41	5	
Whooping-cough	2,781	165	280	76	106	3,002	174	326	71	59

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	0	0			0	*0*	0	*0*	0	0
Dysentery	0	0					0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0				*1*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	11		5		0	*14*		*1*	0	1
Influenza	6	1	4		0	*11*	3	*1*	0	1
Measles		0			1		0	*1*	0	0
Meningococcal infection		0					1	*0*		
Pneumonia	175	30			3	*167*	29		9	10
Poliomyelitis, acute	1	0			0	*1*	0			0
Scarlet fever		0			0		0	*0*	0	0
Tuberculosis:										
Respiratory	90	10	15		9	*127*	11	*21*	2	8
Non-respiratory		2	0		6		2	*5*	0	6
Whooping-cough	3	0			1	*4*	0	*0*	0	0
Deaths 0–1 year	212	25	31		18	*270*	30	*26*	9	20
Deaths (excluding stillbirths)	4,660	688	531		136	*4,784*	704	*535*	115	175
LIVE BIRTHS	7,926	1191	881		505	*8,059*	1254	*944*	244	513
STILLBIRTHS	189	26	28			*211*	21	*25*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

In England and Wales during the week ending May 24 an increase was recorded in the number of notifications of measles 493, and decreases were reported for scarlet fever 118, whooping-cough 124, and dysentery 59.

A small rise in the incidence of measles occurred in most areas of the country. The largest rises were Yorkshire West Riding 146 and Derbyshire 71, while the only large exception to the general trend was a fall of 66 in Suffolk. Only small variations occurred in the returns of whooping-cough. The only fluctuation of any size in the local trends of scarlet fever was a fall of 51 in the number of notifications in Lancashire. The notifications of diphtheria were 2 fewer than in the preceding week. The chief feature of the returns was an increase of 5 in Warwickshire.

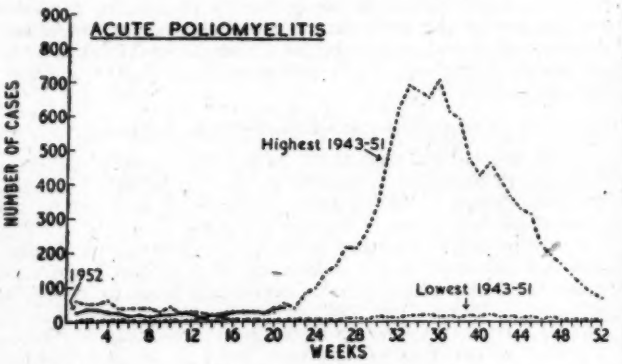
The number of notifications of paratyphoid fever was 31 more than in the previous week, due to outbreaks in Wales. 28 cases were notified in Glamorganshire (Gelligaer U.D. 16) and 15 cases in Monmouthshire (Bedwelty U.D. 8, Mynyddislwyn U.D. 7).

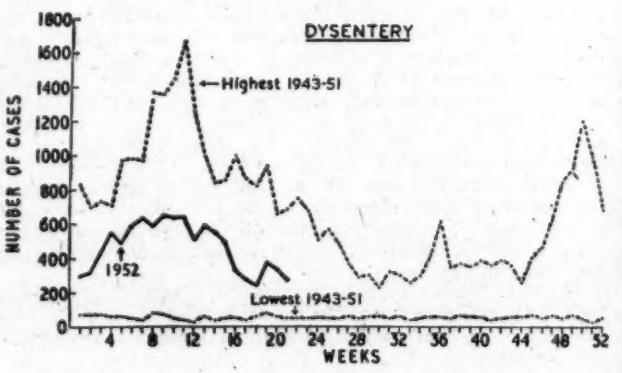
The number of notifications of acute poliomyelitis was 7 fewer for paralytic and 7 more for non-paralytic cases than in the preceding week. The largest returns were Suffolk 6 (Blyth R.D. 5), Middlesex 4 (Ealing M.B. 2), Lancashire 4 (Manchester C.B. 2), London 4.

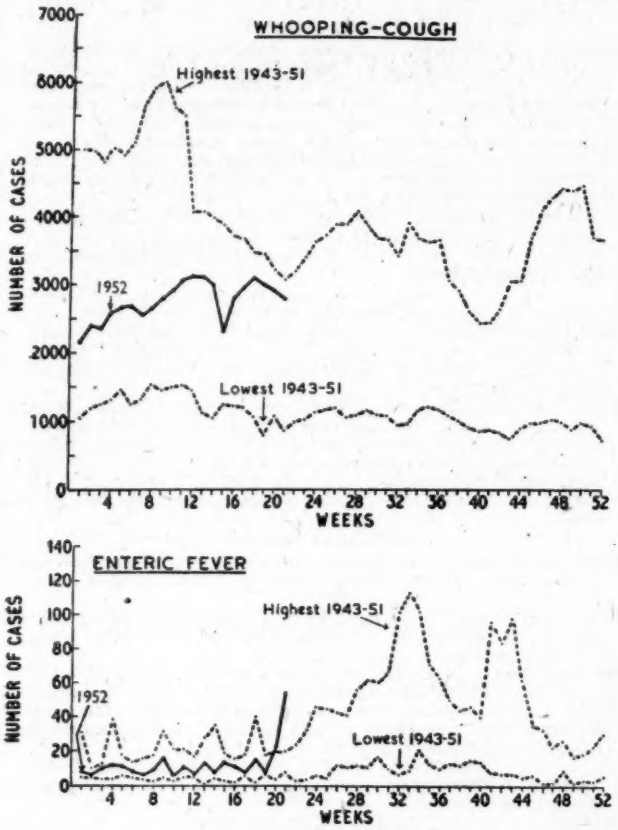
The largest centres of dysentery were: Lancashire 91 (Manchester C.B. 24, Rainford U.D. 12, Oldham C.B. 11), London 38, and Middlesex 19 (Hayes and Harlington U.D. 9).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus -------, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Week Ending May 31

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 915, whooping-cough 2,595, diphtheria 24, measles 6,616, acute pneumonia 380, acute poliomyelitis 44, dysentery 276, paratyphoid fever 45, and typhoid fever 3.

Medical News

Register of Medical Auxiliaries.—Free to medical practitioners, hospitals, local authorities, etc., is the 10th edition of the *Orthopists Section* of the *National Register of Medical Auxiliary Services*, just published by the Board of Registration (B.M.A. House, Tavistock Square, London, W.C.1). The register lists all those trained in the practice and principles of the development of binocular vision in squint, both alphabetically and geographically (including a brief overseas list), and is correct up to March 10 this year. The Board of Registration of Medical Auxiliaries was set up by the B.M.A. in 1933, and prepares registers also of chartered physiotherapists, biophysical assistants, radiographers, dispensing opticians, chiropodists, speech therapists, and dietitians.

Prison Medical Officers.—The annual conference of prison medical officers was held at the Home Office on May 23. At the morning session Dr. Desmond Curran and Dr. Maurice Partridge addressed the conference on psychopathic personality. The afternoon was devoted to a symposium on arson. The conference was opened by Mr. L. W. Fox, chairman of the Prison Commission.

Scottish Society of Anaesthetists.—The annual meeting was held at Dunblane Hotel Hydro, Perthshire, from April 25 till April 27, and 120 members, wives, and guests were present. The executive council for 1952–3 is: president, Dr. T. J. C. MacDonald (Aberdeen); vice-president, Dr. W. M. Shearer (Dundee); hon. secretary, Dr. R. N. Sinclair (Glasgow); and Drs. H. H. Pinkerton (Glasgow), J. D. Robertson (Edinburgh), H. W. C. Griffiths (Edinburgh), A. G. Miller (Glasgow), A. Tindal (Glasgow), J. W. L. Bain (Aberdeen), and M. Muir (Dundee). The president's address dealt with the aliphatic halogens which have anaesthetic possibilities. Isopropyl chloride holds out some promise as an analgesic, and experimental work now proceeding indicates that fluorine compounds merit further study. Dr. M. H. Armstrong Davison, Newcastle-upon-Tyne, was a guest of the society, and spoke on the historical background of the mandrake. The prize which the society is awarding annually for the best paper submitted from a registrar was won by Dr. J. P. Payne, Edinburgh.

Ulster Paediatric Society.—At the annual general meeting on April 2, Dr. Samuel Barron was elected chairman for the year 1952–3. The society also met at the Great Northern Hotel, Rostrevor, on May 23, when Mr. R. Groves, Headmaster of Campbell College, Belfast, spoke on "The Health of the Schoolboy." The annual dinner was held after the meeting.

Commemorating William Hunter.—Miss Dorothea Oliver, great-great-great-niece of William Hunter, on June 7 unveiled a plaque on the Lyric Theatre, Great Windmill Street, London, W.1, commemorating the site of his home and museum. Among those present were Dr. T. B. Jobson, a great-great-great-great-nephew, and his wife, Sir Arthur Porritt, president of the Hunterian Society, Mr. C. Robert Rudolf, honorary curator of the society, Sir Gordon Gordon-Taylor, Dr. Basil Parsons-Smith, and Mr. Alec W. Badenoch. A preliminary announcement about the L.C.C.'s plans to erect the plaque appeared in the *Journal* of May 10 (p. 1020).

Victorian Pennies Appeal.—Sir Harold Kenyon, chairman of the Central Council for District Nursing in London, has appealed to the public to collect Queen Victorian pennies and halfpennies to aid district nursing funds. He said that approximately 457 million pennies and 360 million halfpennies were issued between 1860 and 1901—a potential £2,654,166 for district nursing funds.

Westminster Hospital.—With Dr. A. J. Shinnie in the chair, the Old Students' Dinner of the Westminster Hospital was held in Grosvenor House on June 6. Sir Adolphe Abrahams proposed the hospital and the medical school in a witty speech. The school had grown much since he joined the staff, recruited largely from the major teaching hospitals. Saying that the merits of the school could be assessed by its students, staff, and journal, he paid tribute to all three, mentioning in particular Sir Stanford Cade and Dr. Shinnie, who had recently received the Smith Award of the Royal Institute of Public Health and Hygiene. In proposing the health of the guests, Sir Stanford Cade extolled the merits of one and all. There were three wards in the Westminster, he said, bearing the names of men now living—Lord Wigram, Sir Ernest Rock Carling, and Sir Bernard Docker. Among those present were Lord Wigram, Lord Nathan, Lord Kershaw, the Dean of Westminster, Canon Hildyard, the Mayor of Westminster, and the house governor, Mr. Charles Power. The reply was made by Mr. H. F. C. Crookshank, M.P., the principal guest of the evening, who said that the school stood for tradition, loyalty, and discipline, repeating Disraeli's dictum that a nation was governed either by force or by tradition. Dr. R. S. Taylor proposed the health of the chairman, and Dr. Shinnie replied.

Anglo-French Exchange Bursaries.—The following have been awarded bursaries for special studies in France, under the exchange scheme announced in the *Journal*, March 8 (p. 555): G. W. D. Henderson, consultant pathologist, deputy director Salisbury area pathological service; K. W. Lovel, medical registrar to the thoracic unit, The Hospital for Sick Children, Great Ormond Street, London, W.C.1; F. W. Nash, at present research fellow in paediatrics, Philadelphia Children's Hospital, U.S.A.; J. F. Skone, Elliston Scholar, London School of Hygiene and Tropical Medicine (from October, 1951); E. A. Wright, junior lecturer in pathology at Guy's Hospital (appointed 1949).

NEW ISSUES

British Journal of Social Medicine.—The next issue of this journal (Vol. 6, No. 2) will be available in a week's time. The principal contents include:

STATISTICAL THEORY OF PROPHYLACTIC AND THERAPEUTIC TRIALS—PART I. LIMITATIONS OF THE UNIQUE NULL HYPOTHESIS. Lancelot Hogben and Raymond Wrighton.
THE HEALTH OF AN URBAN COMMUNITY. Lilli Stein and S. A. Sklaroff.
OBSERVATIONS ON ALL BIRTHS (23,970) IN BIRMINGHAM, 1947. VI. BIRTH WEIGHT, DURATION OF GESTATION, AND SURVIVAL RELATED TO SEX. J. R. Gibson and Thomas McKeown.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

Medical and Biological Illustration.—The next issue of this journal (Vol. 2, No. 2) will be available in a week's time. The principal contents include:

THE NOTORNIS EXPEDITION, 1950.
PHOTOGRAPHY AND THE UNIVERSITIES. L. V. Chilton.
THE EVOLUTION OF THE ANIMAL LABYRINTH. Oliver Gray.
HISTOLOGICAL DRAWINGS IN PEN AND INK. Alastair Graham.
LINE DRAWINGS FOR REPRODUCTION. Mary J. Waldron.
CONSTRUCTIONAL MATERIALS FOR LABORATORY WORK. S. W. Bowler.
RECORDING OF EXOPHTHALMOS AND ASSOCIATED EYE SIGNS. Peter Hansell.
THE DEVELOPMENT OF TEACHING MODELS OF *X*-RAY EQUIPMENT. L. G. Idstrom.
THE MODEL II COLOUR TRANSLATING ULTRA-VIOLET MICROSCOPE Edwin H. Land
A CAMERA STAND FOR FILMING EYE OPERATIONS. H. M. Dekking.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

These journals are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

Royal College of Nursing Conference.—The public health section of the College is arranging an open conference in the Cowdray Hall, Henrietta Place, London, W.1, at 2.15 p.m. on Saturday, July 5. The subject is to be the health and welfare of the family, and Professor A. Leslie Banks will speak. The fee for the conference (including tea) is 5s., and those wishing to attend should apply (enclosing remittance) to Miss D. Omond, Royal College of Nursing, Henrietta Place, W.1, as soon as possible.

Princess Tsahai Hospital.—A garden party and bazaar in aid of the Princess Tsahai Memorial Hospital Fund will be held in the grounds of the Holme, Bedford College, Regent's Park, N.W.1, on Tuesday, July 8, from 3 p.m. to 9 p.m. Donations will be acknowledged by the honorary treasurers of the Fund, Lord Horder and Lord Amulree, c/o Messrs. Gould and Prideaux, 88, Bishopsgate, E.C.2. Gifts for the stalls should be sent to the honorary secretary, 3, Charteris Road, Woodford Green, Essex. All doctors and their wives who can be present will be most welcome.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 16

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—At Surgery Lecture Theatre, 5 p.m., "*The Surgery of Urinary Calculi*," by Professor J. Hellström (Stockholm). (See also June 17 and 18.)
●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—4 p.m., "*Cutaneous Allergy*," by Dr. Stephen Gold.
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—3.45 p.m., "*The Salivary Glands*," Arnott Demonstration by Mr. P. H. Mitchiner.
ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.1.—5 p.m., "*Third Nerve Paralysis*," by Dr. T. H. Whittington.

Tuesday, June 17

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—(1) At Surgery Lecture Theatre, 5 p.m., "*The Surgery of Urinary Calculi*," by Professor J. Hellström (Stockholm). (See also June 16 and 18.) (2) At Anatomy Lecture Theatre, 5 p.m., "*Antibiotic Synergism and Antagonism*," Macarthur Postgraduate Lecture by Dr. Ernest Jawetz (California).
ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.—5 p.m., "*Blood Changes in Industrial Disease*," Ernestine Henry Lecture by Dr. R. E. Lane.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, Wandsworth Common, S.W., 8.30 p.m., "*The Diagnosis and Treatment of Paroxysmal Tachycardia*," by Dr. Courtenay Evans.

Wednesday, June 18

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—At Surgery Lecture Theatre, 5 p.m., "*The Surgery of Urinary Calculi*," by Professor J. Hellström (Stockholm). (See also June 16 and 17.)
●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.45 a.m., medical clinical-pathological conference; 3 p.m., "*Phaeochromocytoma: Diagnosis and Treatment*," by Dr. Henry Aranow (Columbia University).
ROYAL EYE HOSPITAL, St. George's Circus, London, S.E.1.—5.30 p.m., "*Congenital Fundus Abnormalities*," by Mr. R. P. Crick.

Thursday, June 19

LEBANON HOSPITAL FOR MENTAL AND NERVOUS DISORDERS.—At Ambassadors' Hotel, Upper Woburn Place, London, W.C., 4.45 p.m., 53rd annual meeting.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 11, Chandos Street, W., 8.30 p.m., annual general meeting.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—4 p.m., "*Pulmonary Hypertension*," by Dr. Paul Wood.
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—3.45 p.m., "*The Larynx*," Arnott Demonstration by Professor R. J. Last.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—5 p.m., lecture-demonstration in psychiatry by Dr. M. A. Partridge.
●WEST LONDON HOSPITAL MEDICAL SCHOOL, 1, Wolverton Gardens, Hammersmith, W.—8.30 p.m., "*The Future of Surgery in the Treatment of Intracranial Haemorrhage*," Alex Simpson Smith Memorial Lecture by Mr. M. A. Falconer.

Friday, June 20

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Erythrodermias*," clinical demonstration by Dr. D. I. Williams.
KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.
LONDON UNIVERSITY.—At University College Hospital Medical School (Lecture Theatre No. 1), University Street, Gower Street, W.C., 5 p.m., "*The Physiology of Uterine Action*," by Professor Hermogenes Alvarez and Professor Roberto Caldeyro-Barcia, University of Montevideo.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.15 a.m., surgical clinical-pathological conference; 2 p.m., "*Ulcerative Colitis*," by Mr. B. N. Brooke; 4 p.m., "*The Surgical Aspects of Acquired Heart Disease*," by Mr. W. P. Cleland.

Saturday, June 21

BIOCHEMICAL SOCIETY.—At School of Biochemistry, Tennis Court Road, Cambridge, 11 a.m., 309th meeting. Scientific papers.

APPOINTMENTS

BROWN, JOHN KERR, M.B., Ch.B., D.P.H., Medical Officer of Health, Boroughs of Greenwich and Deptford.
BUXTON, ST. JOHN D., M.B., B.S., F.R.C.S., Honorary Consultant in Orthopaedic Surgery to Ministry of Pensions.
DENBIGHSHIRE COUNTY COUNCIL.—*District Medical Officer, Eastern No. 1, and Assistant County Medical Officer*, T. Kenrick Hughes, M.B., Ch.B., D.P.H. *Deputy County Medical Officer*, R. G. Davies, M.D., D.P.H. *Assistant County Medical Officer*, Averil J. Smith, M.B., Ch.B.
DURKIN, SHEILA M., M.B., Ch.B., D.P.H., Assistant Medical Officer of Health and School Medical Officer for County Borough of Smethwick.
EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Assistant Anaesthetist to Peterborough Hospital Group*, R. I. Dixon, M.R.C.S., L.R.C.P., D.A. *Anaesthetic Registrar, Peterborough Memorial Hospital*, A. Romagnoli, M.D. *Anaesthetic Registrar, Newmarket General Hospital*, A. R. Ellerker, L.M.S.S.A. *Medical Registrar, United Norwich Hospitals*, J. D. McCreanor, M.B., Ch.B. *Consultant Obstetrician and Gynaecologist in East Suffolk and Ipswich Area*, H. A. Ripman, M.B., B.S., F.R.C.S., M.R.C.O.G. *Surgical Registrar, West Norfolk and King's Lynn General Hospital*, Edward M. Barker, M.B., B.Ch.
FLYNN, MICHAEL P., M.B., B.Ch., D.P.H., County Medical Officer, Roscommon, Eire.
GAVIN, FREDERICK WILLIAM, M.D., D.P.H., Medical Officer of Health, Borough of Richmond and Rural Districts of Croft, Richmond, and Startforth, and Assistant County Medical Officer, North Riding of Yorkshire.
MANCHESTER REGIONAL HOSPITAL BOARD.—*Consultant Physician, Victoria Hospital, Blackpool*, P. R. Duncan, M.B., Ch.B., M.R.C.P. *Consultant Dermatologist, Oldham, Ashton, and Stockport Hospital Centres, and the Manchester and Salford Hospital for Skin Diseases*, J. Curry, M.D. *Consultant Chest Physician, Blackburn and District Hospital Centre*, R. L. Ward, M.D., M.R.C.P. *Consultant Obstetrician/Gynaecologist, Lancaster and Kendal Hospital Centre*, W. P. G. Dickson, M.B., Ch.B.,

M.R.C.O.G. *Assistant Radiologist, Barrow and Furness Hospital Centre,* J. Wilson, M.B., Ch.B., D.M.R.D.

MARTIN, VICTOR DAVID RANDALL, M.B., Ch.B., D.P.H., Medical Officer of Health, Alton Urban and Rural Districts, and Assistant Medical Officer of Health, Hampshire.

SIMPSON, N. R. W., M.B., B.S., D.Phys.Med., Consultant in Physical Medicine, Leicester Royal Infirmary and associated hospitals.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Assistant Chest Physician (S.H.M.O.) to North Gloucestershire Clinical Area,* S. Haczkiewicz, Dip.Med. *Assistant Venereologist (S.H.M.O.) to Bristol, North Gloucestershire, Bath, and South Somerset Clinical Areas,* E. H. Jeanes, M.B., Ch.B., D.P.H. *Consultant Anaesthetist, Bristol Clinical Area,* T. R. Steen, M.B., B.Chir., D.A.

TAYLOR, SELWYN F., M.Ch., F.R.C.S., Surgeon, King's College Hospital, Denmark Hill, London, S.E.

WARD, CECILIA, M.B., B.S., House-surgeon to Gynaecological and Obstetrical Department, Victoria Hospital, Blackpool.

WELSH REGIONAL HOSPITAL BOARD.—*Assistant Psychiatrist, St. Cadoc's Hospital, Caerleon,* D. F. V. Johnston, M.B., B.Ch. *Assistant Chest Physicians, Denbighshire and Flintshire Area,* Jessie E. Wilson, M.B., Ch.B., D.P.H., and J. F. Durrans, M.R.C.S., L.R.C.P. *Medical Officer, for Geriatrics, St. David's Hospital, Cardiff,* G. F. J. Thomas, M.R.C.S., L.R.C.P. *Assistant Chest Physician, Newport and East Monmouth Hospital Committee,* T. L. Hilliard, M.R.C.S., L.R.C.P. *Consultant Obstetrician and Gynaecologist, Clwyd and Deeside,* E. P. Jones, M.B., B.S., M.R.C.O.G. *Assistant Pathologist for West Wales,* C. L. Hollick, M.R.C.S., L.R.C.P. *Registrar in General Surgery, Port Talbot and District General Hospital,* H. M. Sabir, M.B., B.S. *Registrar in General Surgery at Wrexham, Powys, and Mawddach,* R. S. Trueman, M.B., B.S., F.R.C.S.Ed. *Registrar in General Surgery, Bridgend Hospital,* J. Magell, M.B., B.Ch. *Registrar in General Surgery, St. Woolos Hospital, Newport,* D. P. Viljoen, M.R.C.S., L.R.C.P., D.T.M.&H.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Jeffs.—On May 27, 1952, at University College Hospital, London, to Doris, wife of Harry G. Jeffs, M.B., B.S., a daughter—Carolyn Jane.

Lotinga.—On May 26, 1952, at the Maternity Hospital, Leeds, to Kathleen (formerly Dunn), wife of Dr. John Lotinga, of 48, Headingley Lane, Leeds, a son.

Powell.—On May 28, 1952, at the Royal Infirmary, Cardiff, to Elizabeth Jean (formerly Courts), wife of Dr. G. D. Powell, a son.

MARRIAGES

Lamb—Greenaway.—On May 22 1952, at St. Margaret's Church, Rottingdean, Sussex, John Tunstall Lamb, M.B., Ch.B., to Diana Joy Greenway.

DEATHS

Andrews.—On May 29, 1952, at Caton Green Nursing Home, Lancaster, Mary Neville Andrews, M.D., D.T.M.&H., late of China.

Ashton.—On June 3, 1952, at Bronwylfa, Machynlleth, North Wales, John Caradoc Ashton, M.B., Ch.B., aged 78.

Beggs.—On May 28, 1952, at Musgrove Park Hospital, Taunton, Somerset, Herbert Tennyson Beggs, L.R.C.P.&S.I. & L.M., of The Old Vicarage, North Petherton, Bridgwater, Somerset, aged 61.

Boyd.—On June 4, 1952, at Duncliffe, Dunoon, Argyll, John Campbell Boyd, M.D

Czech.—On June 3, 1952, at the Brook General Hospital, London, S.E., Jozef Czech, M.D., aged 39.

Forster.—On May 27, 1952, Robert James Forster, M.R.C.S., L.R.C.P., of Conisbrough, Yorks.

Gill.—On June 5, 1952, at West Malling, Kent, Thomas Paterson Gill, M.B., F.R.C.S.Ed., D.L.O., aged 51.

Green.—On May 30, 1952, in Cornwall, Alexander Percival Green, M.R.C.S., L.R.C.P.

Hartley.—On June 5, 1952, at a London hospital, John Armstrong Hartley, M.D., late of Ticehurst House, Ticehurst, Sussex.

Kastelian.—On June 5, 1952, Solomon Geshel Kastelianski Kastelian, M.D., of Oslo Court, London, N.W.

Mackenzie.—On May 20, 1952, at Aberdeen, Mary Meta Mackenzie, M.B., Ch.B., D.P.H., of 41, Rubislaw Den South, Aberdeen.

Mair.—On June 5, 1952, at Audsley, Swanland, East Yorks, Alexander Middleton Mair, M.B., F.R.C.S., aged 40.

Palser.—On June 1, 1952, John Edwin Ford Palser, M.R.C.S., L.R.C.P., of Southsea, Hants.

Pennefather.—On May 28, 1952, at Byron House, Harrow-on-the-Hill, Middlesex, Claud Maxwell Pennefather, M.D., aged 75.

Pretty.—On May 30, 1952, at 116, Rockingham Road, Kettering, Northants, Harold Cooper Pretty, M.R.C.S., L.R.C.P., aged 76.

Rankin.—On May 19, 1952, at his home, The Elms, Bottesford, Nottingham, James Louis Rankin, M.B., Ch.B.

Ross.—On June 4, 1952, at 26, Dalhousie Terrace, Edinburgh, Frank Ross, M.B., Ch.B., D.T.M.

Ross-Somer.—On May 29, 1952, Margaret Georgina Ross-Somer, M.B., Ch.B., of 14 Blyth Road, Bromley, Kent.

Stock.—On May 30, 1952, at "Dorrington," Porthill, Stoke-on-Trent, William Stuart Vernon Stock, M.B., F.R.C.S., formerly of Clifton, Bristol, aged 79.

Walmsley.—On May 28, 1952, at 3, Deepdene Vale, Dorking Surrey, Stephen Elliott Walmsley, M.R.C.S., L.R.C.P., late of Birmingham.

Warner.—On May 24, 1952, Allan Warner, M.D., D.P.H., of The Cottage, Desford, near Leicester, aged 81.

Willes.—On June 2, 1952, at St. Bartholomew's Hospital, London, E.C., Charles FitzGerald Willes, M.R.C.S., L.R.C.P., Surgeon Lieutenant-Commander, R.N., retired, of Abbots Leigh, near Bristol.

Woodhouse.—On May 29, 1952, at Old Ford House, Blandford St. Mary, Dorset, Francis Decimus Woodhouse, M.R.C.S., L.R.C.P., D.P.H., aged 88.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Prognosis of Perthes's Disease

Q.—*What is the prognosis for untreated Perthes's disease in later life? Are painful episodes likely to become more frequent and severe? Is any treatment worth considering for a mother of several children, who must lead an active life?*

A.—The prognosis for untreated Perthes's disease depends upon the degree to which the head of the femur has become distorted during the stage of softening of the bone. In many cases in which no treatment has been given, and weight has been borne on the limb during the stage of softening, the deformity of the femoral head is serious. In consequence, degenerative osteoarthritis is likely to come on gradually at an unpredictable age, often between 30 and 40. The pain associated with such developing arthritis is likely to be slight and intermittent at first, but later to become more frequent and severe, and it is likely to be made worse by much walking on the limb. While disablement is only moderate, active treatment may not be necessary, and it may be sufficient to advise the patient to lead a less active life. If the disability is more severe, but not bad enough to justify operative treatment, conservative treatment as for osteoarthritis arising from other causes is worth trying: the methods available include various forms of physiotherapy and, according to some authorities, injections of local analgesic or certain acid solutions into the joint, or *x*-ray therapy.

If the disablement becomes severe, so that walking is difficult and very painful, and especially if the pain interferes with sleep, operative treatment should be considered. The main methods available include arthrodesis of the joint, or one of the methods of arthroplasty. The Judet acrylic prosthesis falls into this latter category. The short-term results of this method have been good in a high proportion of cases, but the long-term results are still uncertain, and some authorities consider that cup arthroplasty, in its original or in a modified form, is preferable in relatively young patients.

Gamma Rays and Rheumatism

Q.—*Claims have been made that gamma rays applied locally to the surface of the body are effective in treating rheumatic conditions. Is there any scientific evidence to support these claims?*

A.—It is assumed that the rheumatic conditions to which the question refers include the various forms of chronic arthritis. Radiotherapy is often used in the treatment of osteoarthritis, although the response to treatment is variable and difficult to assess, but this form of treatment is not considered to be of any value in rheumatoid arthritis or the non-articular manifestations of rheumatic disease. Radiotherapy is the accepted form of treatment for ankylosing spondylitis. The aim of treatment in those forms of arthritis which fall within the scope of radiotherapy is the delivery of an adequate dose of ionizing radiation to the affected joint. External irradiation used for this purpose must therefore have sufficient penetration to deliver an appreciable dose to the joint without damaging the intervening skin and subcutaneous tissues. This can be achieved by using high-voltage *x* rays generated at approximately 200 kV. Any attempt to reproduce this effect by the substitution of gamma rays for *x* rays would demand

the use of a very large radioactive source, the handling of which would be dangerous and should be carried out only by workers experienced in this field. There is no scientific evidence that small quantities of gamma rays applied locally to the surface of the body have any material effect in rheumatic disease.

Trophic Ulcers after Infantile Paralysis

Q.—*What is the treatment for the indolent trophic ulcers which develop on the paralysed limb of patients who have had infantile paralysis?*

A.—Indolent ulcers are prone to occur on cold, blue, paralysed limbs of patients who have had infantile paralysis. The ulceration is essentially due to poor circulation. Poor circulation is due in its turn to atrophy of the blood vessels through lack of the vasodilator substances formed by contracting muscles. These ulcers can be cured by improvement in the blood supply to the limb. A lumbar sympathectomy will improve the blood supply by dilating the smaller blood vessels and thus promoting a brisker blood flow. The results of sympathectomy, however, will not last if the limb is completely paralysed owing to the lack of vasodilator substances from muscle contraction. Sympathectomy, therefore, is indicated *only if there is some muscle power in the limb*. In these cases the results are excellent. Where there is no muscle power in the limb, amputation is the best course.

Sterilization During the Puerperium

Q.—*Surgical sterilization by tying the Fallopian tubes is sometimes carried out on the third or fourth day of the puerperium, the argument being that the operation is technically easy at this time. Is it sound practice to perform this operation so soon after delivery?*

A.—It is common practice to carry out tubal sterilization, if indicated, early in the puerperium, but to avoid complications simple ligation is preferable to any procedure involving the resection of the tubes or the burying of the cut ends. The objection to simple ligation on the grounds that the rapid involution in the puerperium may cause the ligature to slip is theoretical rather than practical. The operation is contraindicated if the patient is pyrexial. Also, in the presence of severe heart disease the operation is best deferred, as sudden death in the puerperium is a recognized if uncommon risk in such cases.

There are three advantages of carrying out sterilization in the puerperium. First, as the uterus is then an abdominal organ, only a small infra-umbilical incision is required and the operation is easily and quickly completed. Secondly, the woman is saved a convalescence, as the post-operative period and the puerperium coincide. Thirdly, it commonly happens that a woman, who agrees at the time of delivery to be sterilized some months later, then refuses to re-enter hospital for the operation, hoping that she will not become pregnant again. In such cases the obstetrician may later be faced with the graver medical and surgical problem of having to contemplate a therapeutic abortion as well as sterilization.

Periodic Acne

Q.—*A girl of 23 has a mild acne-like facial rash at each menstrual period. What is the cause, and what treatment is recommended? Is stilboestrol indicated, and, if so, are there any unpleasant side-effects?*

A.—We know that acne is associated with an excessive endogenous secretion of adrenal androgens and can be produced by the administration of testosterone. It appears to be alleviated in some cases by the giving of stilboestrol or other oestrogens. It is possible that progesterone can produce acne, as it is mildly androgenic. The time variations in relationship to the menstrual cycle may be correlated with variations in adrenal and ovarian secretions. Apart from the occasional nausea produced by stilboestrol, large doses may interfere with the regularity of menstruation. Antibiotics are used in addition to oestrogens when a superimposed infection factor is troublesome.

Eczema of the Hand in a Child

Q.—*My granddaughter, aged 9, suffers from a very itching eczema, mostly in the clefts of the fingers and palms of the hands. Various soothing applications have been tried, but with only temporary relief. A few weeks ago she had a mild attack of scarlet fever which practically cleared away the eczema, but it is threatening again. She is in good health otherwise, but sorely troubled with the continual itching. Any suggestion for treatment would be very welcome.*

A.—Eczema of the hands in young children is uncommon, and usually both the search for its cause and the treatment are most difficult. Sensitivity to external contacts is uncommon before puberty, though this possibility should be carefully considered in relation to the history. The fact that the eruption cleared up when the child was ill and presumably confined to bed may indicate that she was, during this period, removed from contact with some source of allergic sensitivity. Another possibility to be considered is photosensitization of the hands acquired by handling some part of a plant. The writer has encountered in a child a case of this sort which resulted from handling cow parsley. This explanation seems unlikely in this case, since such an eruption would not be expected to appear on the palms. A detailed history of exacerbations and remissions may help to clear up these points, but in most cases of this kind in children no cause is found.

Symptomatic treatment is rather unsatisfactory: probably the best applications are those containing 2 or 3% of coal tar in Lassar's paste, zinc cream, or ung. aquosum. It may be sufficient if the ointments are applied at night and cotton gloves worn, and no treatment applied during the day. Radiotherapy may well clear up the condition, but, since its effects are liable to be temporary, it is a measure of doubtful value.

Habitual Abortion

Q.—*Where can I find information on how habitual abortion should be treated?*

A.—On p. 160 of the book "*Any Questions?*" The book can be obtained for 7s. 6d. (postage 6d.) from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

NOTES AND COMMENTS

Treatment of Lightning Pains.—Dr. A. O. Ross (Liverpool) writes: With reference to the question on the treatment of lightning pains ("Any Questions?" May 17, p. 1091), the following deep subcutaneous injection often proves useful, and one course of 50 daily injections may cause long remission:

℞	Mercury oxycyanide	0.5 mg.
	Atropine sulphate	0.5 mg.
	0.5% solution of procaine	to 1 ml.

It can be dispensed in rubber-capped phials of 50 ml. to give a complete course.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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